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PRIORITY DOCUMENT

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Dated 26 OCT 1995

For official use

28 APR 1995

Your reference
RJG/JLB/177

28 APR 1995

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Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700)

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form

The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: NEW COMPOUND

❷ Applicant's details

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required

❑ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: FUJISAWA PHARMACEUTICAL CO LTD

Country *(and State of incorporation, if appropriate)*: JAPAN

2b If you are applying as an individual or one of a partnership please give in full

Surname

Forenames

2c **In all cases**, please give the following details:

Address: 4-7 DOSHOMACHI 3-CHOME
CHUO-KU, OSAKA-SHI
OSAKA 541, JAPAN

UK postcode *(if applicable)*

Country: JAPAN

ADP number *(if known)*: 04034831001

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2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

☐ **Second applicant *(if any)***

2d If you are applying as a corporate body please give:

Corporate name

Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

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Forenames

2f **In all cases**, please give the following details:

Address

UK postcode *(if applicable)*

Country

ADP number *(if known)*

---

❹ An address for service in the United Kingdom must be supplied

Please mark correct box

❹ Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ ***go to 3b***

↓ ***please give details below***

Agent's name STEVENS, HEWLETT & PERKINS

Agent's address 1 SERJEANTS' INN
FLEET STREET
LONDON

Postcode EC4Y 1LL

Agent's ADP number 1545003 ✓

3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Daytime telephone number *(if available)*

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ADP number *(if known)*

❹ Reference number

4 Agent's or applicant's reference number *(if applicable)* RJG/JLB/177

❺ Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No [X] ➡ ***go to 6***

⬇ ***please give details below***

❑ number of earlier application or patent number

❑ filing date *(day month year)*

❑ and the Section of the Patents Act 1977 under which you are claiming

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

❻ Declaration of priority

❻ *If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.*

Please give the date in all number format, for example, 31/05/90 for 31 May 1990

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day, month, year)*

❼ *The answer must be 'No' if:*
- *any applicant is not an inventor*
- *there is an inventor who is not an applicant, or*
- *any applicant is a corporate body.*

❼ Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes [ ] No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			
Claim(s)	20	Description	89
Abstract		Drawing(s)	

Please mark correct box(es)

8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 – Preliminary Examination/Search	
Patents Form 10/77 – Request for Substantive Examination	

❾ *You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request*

❾ Request

I/We request the grant of a patent on the basis of this application.

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Signed Stevens, Hewlett & Perkins Date 28 (day) 04 (month) 95 (year)

AGENTS FOR THE APPLICANT

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NEW COMPOUND

The present invention relates to new polypeptide compound and a pharmaceutically acceptable salt thereof.

More particularly, it relates to new polypeptide compound and a pharmaceutically acceptable salt thereof, which have antimicrobial activities (especially, antifungal activities), inhibitory activity on β-1,3-glucan synthase, and further which are expected to be useful for the prophylactic and/or therapeutic treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

Accordingly, one object of the present invention is to provide new polypeptide compound and a pharmaceutically acceptable salt thereof, which are highly active against a

number of pathogenic microorganisms and further which are expected to be useful for the prophylactic and/or therapeutic treatment of Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal.

Another object of the present invention is to provide a process for the preparation of new polypeptide compound and a salt thereof.

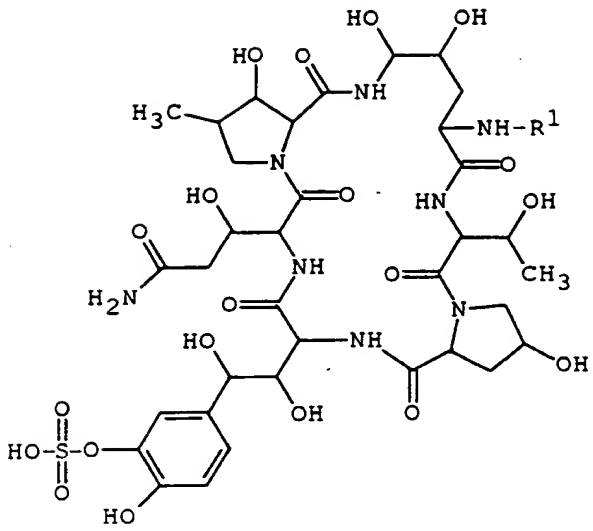
A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said new polypeptide compound or a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a method for the prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) caused by pathogenic microorganisms, which comprises administering said new polypeptide compound or a pharmaceutically acceptable salt thereof to a human being or an animal.

An additional object of the present invention is to provide a use of said new polypeptide compound and a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the prophylactic and/or therapeutic treatment of above-mentioned diseases in a human being or an animal.

A still additional object of the present invention is to provide a use of said new polypeptide compound and a pharmaceutically acceptable salt thereof for the prophylactic and/or therapeutic treatment of above-mentioned diseases in a human being or an animal.

The object polypeptide compound used in the present invention are new and can be represented by the following general formula [I] :



[I]

wherein R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

3 to 8 membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy;

ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s);

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclic(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

aryloxy(lower)alkanoyl which may have one or more suitable substituent(s);

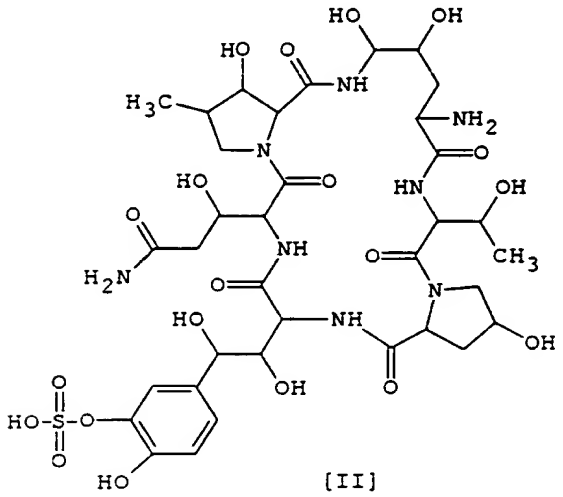
ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s); or

arylamino(lower)alkanoyl which may have one or more suitable substituent(s).

one or more suitable substituent(s).

The new polypeptide compound [I] and a pharmaceutically acceptable salt thereof can be prepared by the process as illustrated in the following reaction scheme.

Process 1

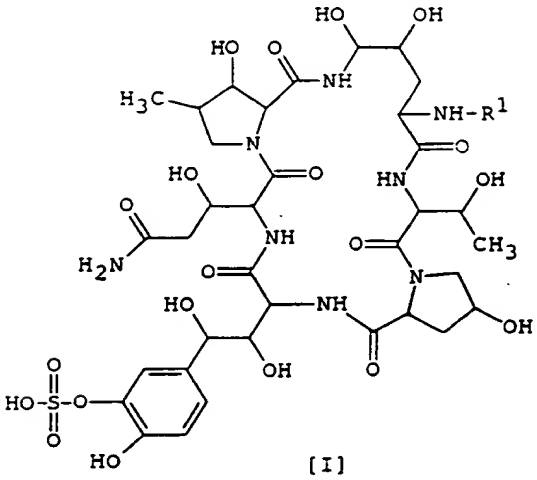


[II]

or its reactive derivative at the amino group or a salt thereof

R^1-OH [III]

or its reactive derivative at the carboxy group or a salt thereof



[I]

or a salt thereof

wherein R^1 is as defined above.

Suitable pharmaceutically acceptable salts of the object polypeptide compound [I] are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 3.

Suitable example of "lower alkanoyl" may include

straight or branched one such as formyl, acetyl, 2-methylacetyl, 2,2-dimethylacetyl, propionyl, butyryl, isobutyryl, pentanoyl, 2,2-dimethylpropionyl, hexanoyl, and the like.

Suitable example of "suitable substituent(s)" in the groups such as "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)", "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)", etc. may include lower alkoxy as mentioned below, higher alkoxy as mentioned below, lower alkyl as mentioned below, higher alkyl as mentioned below, higher alkoxy(lower)alkyl, lower alkoxycarbonyl, oxo, aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl which may have one or more lower alkyl, aryl which may have one or more higher alkyl, aryl substituted with aryl which may have one or more lower alkoxy, aryl substituted with aryl which may have one or more higher alkoxy, aryl substituted with aryl which may have one or more lower alkyl, aryl substituted with aryl which may have one or more higher alkyl, aroyl which may have one or more lower alkoxy, aroyl which may have one or more higher alkoxy, aroyl which may have one or more lower alkyl, aroyl which may have one or more higher alkyl, heterocyclic group which may have one or more lower alkoxy, heterocyclic group which may have one or more higher alkoxy, aryl having heterocyclic(higher)alkoxy, and the like.

Suitable example of "lower alkoxy" may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, and the like, in which the preferred one may be (C_3-C_6)alkoxy, and more preferred one may be butoxy, pentyloxy, and hexyloxy.

Suitable example of "higher alkoxy" may include straight or branched one such as heptyloxy, octyloxy, 3,5-dimethyloctyloxy, 3,7-dimethyloctyloxy, nonyloxy, decyloxy, undecyloxy, dodecyloxy, tridecyloxy, tetradecyloxy, hexadecyloxy, heptadecyloxy, octadecyloxy, nonadecyloxy, icosyloxy, and the like,

in which the preferred one may be (C_7-C_{14})alkoxy, and the more preferred one may be heptyloxy and octyloxy.

Suitable example of "lower alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, and the like,

in which the preferred one may be methyl, pentyl and hexyl.

Suitable example of "higher alkyl" may include straight or branched one having 7 to 20 carbon atoms, such as heptyl, octyl, 3,5-dimethyloctyl, 3,7-dimethyloctyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, and the like,

in which the preferred one may be (C_7-C_{14})alkyl, and the more preferred one may be heptyl, octyl and nonyl.

Suitable example of "aryl" and "ar" moiety may include phenyl which may have lower alkyl (e.g., phenyl, mesityl, tolyl, etc.), naphthyl, anthryl, and the like,

in which the preferred one may be phenyl and naphthyl.

Suitable example of "aroyl" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl, and the like,

in which the preferred one may be benzoyl and naphthoyl.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)"

can be referred to aforementioned "lower alkanoyl", in which the preferred one may be (C_1-C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom" in the term of "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl (e.g., 4H-1,2,4-triazinyl, 1H-1,2,3-triazinyl, etc.), tetrazinyl (e.g., 1,2,4,5-tetrazinyl, 1,2,3,4-tetrazinyl, etc.), and the like,

in which the preferred one may be unsaturated 6-membered heteromonocyclic group containing 1 to 3 nitrogen atom(s), and the most preferred one may be pyridyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic groups containing at least one nitrogen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be higher alkoxy and higher alkoxy(lower)alkyl, and the more preferred one may be (C_7-C_{14})alkoxy and (C_7-C_{14})alkoxy(C_1-C_4)alkyl, and the most preferred one may be octyloxy and octyloxymethyl.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1-C_4)-alkanoyl, and the more preferred one may be formyl.

Suitable example of "suitable substituent(s)" in the

term of "lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl and lower alkoxycarbonyl, and the more preferred one may be (C_7-C_{14})alkoxy and (C_1-C_4)alkoxycarbonyl, and the most preferred one may be octyloxy and tert-butoxycarbonyl.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1-C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing at least one oxygen atom" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" may include unsaturated condensed heterocyclic group containing one or more oxygen atom(s) and, optionally, another hetero atom(s) except oxygen atom,

in which the preferred one may be unsaturated condensed heterocyclic group containing 1 to 3 oxygen atom(s), unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 2 sulfur atom(s) and unsaturated condensed heterocyclic group 1 to 3 oxygen atom(s) and 1 to 3 nitrogen atom(s), and the more preferred one may be benzo[b]furanyl, isobenzofuranyl, chromenyl, xanthenyl, benzoxazolyl, benzoxadiazolyl, dihydrooxathiinyl, phenoxathiinyl, and the like, and the most preferred one may be benzo[b]furanyl, chromenyl and benzoxazolyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl and oxo, and the more preferred one may be (C_7-C_{14})alkoxy, (C_1-C_4)alkyl, (C_7-C_{14})alkyl and oxo, and the most preferred one may be octyloxy, methyl, nonyl, and oxo.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1-C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" may include unsaturated condensed heterocyclic group containing only 1 to 3 sulfur atom(s),

in which the preferred one may be benzothienyl and benzodithiinyl, and the most preferred one may be benzothienyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher

alkoxy, lower alkyl and higher alkyl, and more preferred one may be (C_7-C_{14})alkoxy, and the most preferred one may be octyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1-C_4)alkanoyl, and the most preferred one may be formyl.

Suitable example of "unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" may include 1H-indazolyl, purinyl, phthalazinyl, benzoimidazolyl, naphthyridinyl, quinoxalinyl, quinazolyl, cinnolinyl, peteridinyl, and the like,

in which the most preferred one may be benzoimidazolyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, aryl which may have one or more lower alkoxy and aryl which may have one or more higher alkoxy, and the more preferred one may be (C_7-C_{14})alkyl and phenyl which may have 1 to 3 (C_1-C_6)alkoxy, and the most preferred one may be nonyl and phenyl which may have 1 to 3 hexyloxy.

Suitable example of "lower alkanoyl" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered

heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl", in which the preferred one may be (C_1-C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, pyrazolidinyl, morpholinyl, thiomorpholinyl, and the like, in which the preferred one may be piperidyl and piperazinyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s)" may include lower alkoxy, higher alkoxy, higher alkoxy(lower)alkyl, lower alkyl, higher alkyl, oxo, aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl which may have one or more lower alkyl, aryl which may have one or more higher alkyl, aroyl which may have one or more lower alkoxy, aroyl which may have one or more higher alkoxy, aroyl which may have one or more lower alkyl, aroyl which may have one or more higher alkyl, and the like, in which the preferred one may be aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aroyl which may have one or more lower alkoxy and aroyl which may have one or more higher alkoxy, and the

more preferred one may be aryl which may have 1 to 3 higher alkoxy and aroyl which may have 1 to 3 higher alkoxy, and the much more preferred one may be phenyl which may have 1 to 3 (C_7-C_{14})alkoxy and naphthoyl which may have 1 to 3 (C_7-C_{14})alkoxy, and the most preferred one may be phenyl which may have 1 to 3 octyloxy and naphthoyl which may have 1 to 3 heptyloxy.

Suitable example of "ar(lower)alkenoyl" in the term of "ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s)" may include phenyl(lower)alkenoyl (e.g., 3-phenylacryloyl, (2- or 3- or 4-)phenyl-(2- or 3-)butenoyl, 3-phenylmethacryloyl, (2- or 3- or 4- or 5-)phenyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)phenyl-(2- or 3- or 4- or 5-)-hexanoyl, etc.), naphthyl(lower)alkenoyl (e.g., 3-naphthylacryloyl, (2- or 3- or 4-)naphthyl-(2- or 3-)butenoyl, (2- or 3- or 4- or 5-)naphthyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)naphthyl-(2- or 3- or 4- or 5-)hexanoyl, etc.), and the like, in which the preferred one may be 3-phenylacryloyl.

Suitable example of "suitable substituent(s)" in the term of "ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)", in which the preferred "aryl which may have one or more suitable substituent(s)" may be aryl which may have one or more lower alkoxy, aryl which may have one or more lower alkyl and aryl which may have one or more higher alkyl, and the much more preferred one may be phenyl which may have 1 to 3 (C_1-C_6)alkoxy, phenyl which may have 1 to 3 (C_1-C_6)alkyl and phenyl which may have 1 to 3 (C_7-C_{14})alkyl, and the most preferred one may be phenyl which may have 1 to 3 pentyloxy, phenyl which may have 1 to 3 heptyl and phenyl which may have 1 to 3 pentyl.

Suitable example of "naphthyl(lower)alkenoyl" in the

term of "naphthyl(lower)alkenoyl which may have one or more higher alkoxy" may include 3-naphthylacryloyl, (2- or 3- or 4-)naphthyl-(2- or 3-)butenoyl, (2- or 3- or 4- or 5-)naphthyl-(2- or 3- or 4-)pentanoyl, (2- or 3- or 4- or 5- or 6-)naphthyl-(2- or 3- or 4- or 5-)hexanoyl, and the like,

in which the preferred one may be 3-naphthylacryloyl.

Suitable example of "lower alkynoyl" in the term of "lower alkynoyl which may have one or more suitable substituent(s)" may include 2-propynoyl, (2- or 3-)butynoyl, (2- or 3- or 4-)pentynoyl, (2- or 3- or 4- or 5-)hexynoyl, and the like,

in which the preferred one may be 2-propynoyl.

Suitable example of "suitable substituent(s)" in the term of "lower alkynoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be aryl which may have one or more lower alkoxy, aryl which may have one or more higher alkoxy, aryl substituted with aryl which may have one or more lower alkyl and aryl substituted with aryl which may have one or more higher alkyl, and the more preferred one may be aryl substituted with aryl which may have 1 to 3 lower alkyl and aryl which may have 1 to 3 higher alkoxy, and the much more preferred one may be phenyl substituted with phenyl which may have 1 to 3 (C_1-C_6)alkyl and phenyl which may have 1 to 3 (C_7-C_{14})alkoxy, and the most preferred one may be phenyl substituted with phenyl which may have 1 to 3 pentyl and naphthyl which may have 1 to 3 heptyloxy.

Suitable example of "ar(C_2-C_6)alkanoyl" in the term of "ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s)" may include phenyl(C_2-C_6)alkanoyl (e.g., phenylacetyl, (2- or 3-phenylpropanoyl, 2- or 3- or 4-phenylbutanoyl, 2- or 3- or

4- or 5-)phenylpentanoyl, (2- or 3- or 4- or 5- or 6-phenylhexanoyl, etc.}, naphthyl(C_2-C_6)alkanoyl (e.g. naphthylacetyl, (2- or 3-)naphthylpropanoyl, (2- or 3- or 4-)naphthylbutanoyl, (2- or 3- or 4- or 5-naphthylpentanoyl, (2- or 3- or 4- or 5- or 6-naphthylhexanoyl, etc.}, and the like,

in which the preferred one may be 3-phenylpropanoyl.

Suitable example of "suitable substituent(s)" in the term of "ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s)" may include lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, oxo, aryl having one or more lower alkoxy, aryl having one or more higher alkoxy, aryl having one or more lower alkyl, aryl having one or more higher alkyl, aryl substituted with aryl having one or more lower alkoxy, aryl substituted with aryl having one or more higher alkoxy, aryl substituted with aryl having one or more lower alkyl, aryl substituted with aryl having one or more higher alkyl, and the like,

in which the preferred one may be aryl having 1 to 3 lower alkoxy, aryl having 1 to 3 higher alkoxy, aryl having 1 to 3 lower alkyl and aryl having 1 to 3 higher alkyl, and the much more preferred one may be phenyl having 1 to 3 (C_1-C_6)alkoxy and phenyl having 1 to 3 (C_1-C_6)alkyl and the most preferred one may be phenyl having 1 to 3 pentyloxy and phenyl having 1 to 3 pentyl.

Suitable example of "(C_2-C_6)alkanoyl" in the term of "(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy" may include acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, and the like,

in which the preferred one may be propanoyl.

Suitable example of "aroyl" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)" may include benzoyl, toluoyl, naphthoyl, and the like,

in which the preferred one may be benzoyl.

Suitable example of "heterocyclic group" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)" may include unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur

atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like,

in which the preferred one may be saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) and the most preferred one may be piperazinyl and isoxazolyl.

Suitable example of "suitable substituent(s)" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)", in which the preferred one may be aryl which may have 1 to 3 higher alkoxy, and aryl which may have 1 to 3 lower alkoxy, and the more preferred one may be phenyl which may have 1 to 3 (C_7-C_{14})alkoxy, phenyl which may have 1 to 3 (C_3-C_6)alkoxy, and the most preferred one may be phenyl which may have 1 to 3 octyloxy, phenyl which may have 1 to 3 pentyloxy, and phenyl which may have 1 to 3 hexyloxy.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like,
in which the preferred one may be benzoyl.

Suitable example of "heterocyclic" moiety in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy" can be referred to the ones as exemplified before for "heterocyclic group" in the term of "aroyl substituted with heterocyclic group which may have one or more suitable substituent(s)",
in which the preferred one may be unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), and the most preferred one may be triazolyl.

Suitable example of "(higher)alkoxy" in the term of "aroyl substituted with aryl having heterocyclic(higher)-alkoxy" can be referred aforementioned higher alkoxy,
in which the preferred one may be (C_7-C_{14})alkoxy, and the most preferred one may be octyloxy.

Suitable example of "aryl" in the term of "aroyl substituted with aryl having heterocyclic(higher)alkoxy" can be referred to aforementioned "aryl",
in which the preferred one may be phenyl.

Suitable example of "aroyl" in the term of "aroyl

may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like,

in which the preferred one may be benzoyl.

Suitable example of "aryl" in the term of "aroyl substituted with aryl having lower alkoxy(higher)alkoxy" can be referred to aforementioned "aryl",

in which the preferred one may be phenyl.

Suitable example of "lower alkoxy(higher)alkoxy" in the term of "aroyl substituted with aryl having lower alkoxy(higher)alkoxy" may be methoxyheptyloxy, methoxyoctyloxy, methoxynonyloxy, methoxydecyloxy, ethoxyheptyloxy, ethoxyoctyloxy, ethoxynonyloxy, ethoxydecyloxy, ethoxyundecyloxy, propoxyundecyloxy, butoxydodecyloxy, pentyloxytridecyloxy, hexyloxytetradecyloxy, propoxyheptyloxy, propoxyoctyloxy, propoxynonyloxy, butoxydecyloxy, or the like, in which the preferred one may be (C_1-C_6)alkoxy(C_7-C_{14})alkoxy, and the more preferred one may be methoxyoctyloxy.

Suitable example of "aroyl" in the term of "aroyl substituted with aryl having lower alkenyl(lower)alkoxy" may include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like,

in which the preferred one may be benzoyl.

Suitable example of "aryl" in the term of "aroyl substituted with aryl having lower alkenyl(lower)alkoxy" can be referred to aforementioned "aryl",

in which the preferred one may be phenyl.

Suitable example of "lower alkenyl(lower)alkoxy" in the term of "aroyl substituted with aryl having lower alkenyl(lower)alkoxy" may be vinylmethoxy, vinylethoxy, vinylpropoxy, vinylbutoxy, vinylpentyloxy, vinylhexyloxy, 1-(or 2-)propenylmethoxy, 1-(or 2-)propenylethoxy, 1-(or 2-)propenylpropoxy, 1-(or 2-)propenylbutoxy, 1-(or 2-)-propenylpentyloxy, 1-(or 2-)propenylhexyloxy, 1-(or 2- or 3-)butenylbutoxy, 1-(or 2- or 3-)butenylhexyloxy, 1-(or 2-

3-)butenylbutoxy, 1-(or 2- or 3-)butenylhexyloxy, 1-(or 2- or 3- or 4-)pentenylpentyloxy, 1-(or 2- or 3- or 4-)-pentenylhexyloxy, 1-(or 2- or 3- or 4- or 5-)-hexenylbutoxy, 1-(or 2- or 3- or 4- or 5-)hexenylhexyloxy, or the like,

in which the preferred one may be (C_2-C_6)alkenyl(C_1-C_6)alkoxy, and the more preferred one may be vinylhexyloxy.

Suitable example of "aroyl substituted with 2 lower alkoxy" may include benzoyl substituted with 2 lower alkoxy and naphthoyl substituted with 2 lower alkoxy,

in which the preferred one may be benzoyl substituted with 2 (C_1-C_6)alkoxy, and the most preferred one may be benzoyl substituted with 2 pentyloxy.

Suitable example of "aroyl substituted with aryl having lower alkyl" may include benzoyl substituted with phenyl having lower alkyl, benzoyl substituted with naphthyl having lower alkyl, naphthoyl substituted with phenyl having lower alkyl, naphthoyl substituted with naphthyl having lower alkyl, and the like,

in which the preferred one may be benzoyl substituted with phenyl having (C_1-C_6)alkyl, and the most preferred one may be benzoyl substituted with phenyl having hexyl.

Suitable example of "aroyl substituted with aryl having higher alkyl" may include benzoyl substituted with phenyl having higher alkyl, benzoyl substituted with naphthyl having higher alkyl, naphthoyl substituted with phenyl having higher alkyl, naphthoyl substituted with naphthyl having higher alkyl, and the like,

in which the preferred one may be benzoyl substituted with phenyl having (C_7-C_{14})alkyl, and the most preferred one may be benzoyl substituted with phenyl having heptyl.

Suitable example of "aryloxy" moiety in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenoxy, mesityloxy,

tolyloxy, naphthyloxy, anthryloxy, and the like,
in which the preferred one may be phenoxy.

Suitable example of "lower alkanoyl" moiety in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",
in which the preferred one may be formyl, acetyl, 2,2-dimethylacetyl, propionyl, butyryl, isobutyryl and pentanoyl, hexanoyl, and the more preferred one may be (C_1-C_6)alkanoyl, and the much more preferred one may be formyl, acetyl, propionyl and 2,2-dimethylacetyl.

Suitable example of "suitable substituent(s)" in the term of "aryloxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",
in which the preferred one may be (C_7-C_{14})alkoxy, and the more preferred one may be octyloxy.

Suitable example of "ar(lower)alkoxy" moiety in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenyl(lower)alkoxy {e.g., phenylmethoxy, (1- or 2-phenylethoxy, phenylpropoxy, 2-phenyl-1-methylpropoxy, 3-phenyl-2,2-dimethylpropoxy,
(1- or 2- or 3- or 4-)phenylbutoxy, (1- or 2- or 3- or 4- or 5-)phenylpentyloxy, (1- or 2- or 3- or 4- or 5- or 6-phenylhexyloxy, etc.}, naphthyl(lower)alkoxy {e.g. naphthylmethoxy, (1- or 2-)napthylethoxy, 1-naphthylpropoxy, 2-naphthyl-1-methylpropoxy, 3-naphthyl-2,2-dimetyylpropoxy, (1- or 2- or 3- or 4-)naphthylbutoxy, (1- or 2- or 3- or 4- or 5-)naphthylpentyloxy, (1- or 2- or 3- or 4- or 5- or 6-)naphthylhexyloxy, etc.}, and the like,
in which the preferred one may be naphthyl(C_1-C_4)alkoxy, and the more preferred one may be naphthylmethoxy.

Suitable example of "(lower)alkanoyl" moiety in the

term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1-C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "suitable substituent(s)" in the term of "ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl and higher alkyl, and the more preferred one may be higher alkoxy, and the much more preferred one may be (C_7-C_{14})alkoxy, and the most preferred one may be heptyloxy.

Suitable example of "arylamino" moiety in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" may include phenylamino, mesitylamino, tolylamino, naphthylamino, anthrylamino and the like,

in which the preferred one may be phenylamino and naphthylamino.

Suitable example of "lower alkanoyl" in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "lower alkanoyl",

in which the preferred one may be (C_1-C_4)alkanoyl, and the more preferred one may be formyl.

Suitable example of "suitable substituent(s)" in the term of "arylamino(lower)alkanoyl which may have one or more suitable substituent(s)" can be referred to aforementioned "suitable substituent(s)",

in which the preferred one may be lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, aryl which may have 1 to 3 lower alkoxy and aryl which may have 1 to 3 higher alkoxy, and the more preferred one may be (C_7-C_{14})alkoxy,

and phenyl which may have 1 to 3 (C_7-C_{14})alkoxy, and the most preferred one may be heptyloxy and phenyl which may have 1 to 3 heptyloxy.

The process for preparing the object polypeptide compound [I] or a salt thereof of the present invention are explained in detail in the following.

Process 1

The object polypeptide compound [I] or a salt thereof can be prepared by reacting the compound [II] or its reactive derivative at the amino group or a salt thereof with the compound [III] or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound [III] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivaric acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.]; or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester,

propargyl ester,
p-nitrophenyl ester, 2,4-dinitrophenyl ester,
trichlorophenyl ester, pentachlorophenyl ester,
mesylphenyl ester, phenylazophenyl ester, phenyl
thioester, p-nitrophenyl thioester, p-cresyl thioester,
carboxymethyl thioester, pyranyl ester, pyridyl ester,
piperidyl ester, 8-quinolyl thioester, etc.], or an ester
with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine,
1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide,
N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.],
and the like. These reactive derivatives can optionally
be selected from them according to the mind of the
compound [III] to be used.

Suitable salts of the compound [III] and its reactive derivative can be referred to the ones as exemplified for the object polypeptide compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [III] is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene;

1-alkoxy-2-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g., ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorous oxychloride, methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, di(lower)alkylaminopyridine (e.g., 4-dimethylaminopyridine, etc.), N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

The starting compound [II] is a known compound. It can be prepared by fermentation and synthetic processes disclosed in EP 0462531 A2.

A culture of Coleophoma sp. F-11899, which is used in said fermentation process, has been deposited with National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology (former name: Fermentation Research Institute Agency of Industrial Science and Technology) (1-3, Higashi 1-chome, Tsukuba-shi, IBARAKI 305, JAPAN) on October 26, 1989 under the number of FERM BP-2635.

The compounds obtained by the above Process 1 can be isolated and purified by a conventional method such as pulverization, recrystallization, column-chromatography, high-performance liquid chromatography (HPLC), reprecipitation, or the like.

The compounds obtained by the above Process 1 may be obtained as its hydrate, and its hydrate is included within the scope of this invention.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

Biological property of the polypeptide compound [I] of the present invention

In order to show the usefulness of the polypeptide compound [I] of the present invention, the biological data of the representative compound is explained in the following.

Test 1 (Antimicrobial activity) :

In vitro antimicrobial activity of the compound of Example 1 (17) disclosed later was determined by the two-fold agar-plate dilution method as described below.

Test Method

One loopful of an overnight culture of each test microorganism in Sabouraud broth containing 2% Glucose (10^5 viable cells per ml) was streaked on yeast nitrogen base dextrose agar (YNBDA) containing graded

the minimal inhibitory concentration (MIC) was expressed in terms of μg/ml after incubation at 30°C for 24 hours.

Test Result

MIC (μg/ml)

Test compound / Test organism	The compound of Example 1(17)
candida albicans FP-633	0.2

From the test result, it is realized that the object polypeptide compound [I] of the present invention has an antimicrobial activity (especially, antifungal activity).

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid from, which contains the object polypeptide compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams, ointments; aerosols; powders for insufflation;

creams, ointments; aerosols; powders for insufflation; in a liquid form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents; perfumes or buffer; or any other commonly may be used as additives.

The object polypeptide compound [I] or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired antimicrobial effect upon the process or condition of diseases.

For applying the composition to human, it is preferable to apply it by intravenous, intramuscular, pulmonary, oral administration, or insufflation. While the dosage of therapeutically effective amount of the object polypeptide compound [I] varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01-20 mg of the object polypeptide compound [I] per kg weight of human being in the case of intramuscular administration, a daily dose of 0.1-20 mg of the object polypeptide compound [I] per kg weight of human being, in case of oral administration, a daily dose of 0.5-50 mg of the object polypeptide compound [I] per kg weight of human being is generally given for treating or preventing infectious diseases.

Especially in case of the treatment of prevention of <u>Pneumocystis carinii</u> infection, the followings are to be noted.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized as powders which may be formulated and the powder

compositions may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation aerosol, which may be formulated as a suspension or solution of compound in suitable propellants such as fluorocarbons or hydrocarbons.

Because of desirability to directly treat lung and bronchi, aerosol administration is a preferred method of administration. Insufflation is also a desirable method, especially where infection may have spread to ears and other body cavities.

Alternatively, parenteral administration may be employed using drip intravenous administration.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

To a suspension of 1-(4-hydroxyphenyl)-4-tert-butoxycarbonylpiperazine (3 g) and potassium carbonate (0.82 g) in N,N-dimethylformamide (15 ml) was added octyl bromide (1.87 ml). The mixture was stirred for 10 hours at 70°C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel, and eluted with (hexane : ethyl acetate = 9:1). The fractions containing the object compound were combined, and evaporated under reduced pressure to give 1-(4-n-octyloxyphenyl)-4-tert-butoxycarbonylpiperazine (2.71 g).

IR (KBr) : 1687, 1513, 1241 cm^{-1}

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=6.2Hz), 1.2-1.4 (10H, m), 1.48 (9H, s), 1.65-1.85 (2H, m), 3.00 (4H, t, J=5.2Hz), 3.57 (4H, t, J=5.2Hz), 3.90 (2H, t, J=6.5Hz), 6.83 (2H, dd, J=6.4 and 2.1Hz), 6.89 (2H, dd, J=6.4 and 2.1Hz)

Preparation 2

A solution of 1-(4-n-octyloxyphenyl)-4-tert-butoxycarbonylpiperazine (2.61 g) in trifluoroacetic acid (20 ml) was stirred for 4 hours at ambient temperature. The reaction mixture was evaporated under reduced pressure, and to the residue was added a mixture of 1N NaOH aqueous solution and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-(4-n-octyloxyphenyl)piperazine (0.86 g).

IR (KBr) : 2923, 1513, 1259, 831 cm^{-1}

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=6.4Hz), 1.2-1.53

(10H, m), 1.65-1.85 (2H, m), 3.03 (4H, s), 3.90 (2H, t, J=6.5Hz), 6.83 (2H, dd, J=6.4 and 2.9Hz), 6.90 (2H, dd, J=6.4 and 2.9Hz)

APCI-MASS : e/z = 291 (M^++1)

Preparation 3

To a suspension of 1-(4-n-octyloxyphenyl)piperazine (1 g) and potassium carbonate (0.476 g) in N,N-dimethylformamide (1 ml) was added p-fluorobenzonitrile (0.347 g), and stirred for 5 hours at 160°C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-(4-n-octyloxyphenyl)piperazin-1-yl]benzonitrile (0.93 g).

IR (KBr) : 2848, 2217, 1604, 1511, 1241 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.8Hz), 1.2-1.53 (10H, m), 1.65-1.85 (2H, m), 3.20 (4H, t, J=5.4Hz), 3.48 (4H, t, J=5.4Hz), 3.91 (2H, t, J=6.5Hz), 6.8-7.0 (6H, m), 7.52 (2H, d, J=8.9Hz)

APCI-MASS : e/z = 392 (M^++1)

Preparation 4 (1)

A mixture of 2,4-dihydroxybenzaldehyde (5.52 g), potassium carbonate (6.08 g) and octyl bromide (7.73 g) in acetonitrile (55 ml) was stirred for 16 hours at 60°C. The solvent of reaction mixture was removed under reduced pressure, and the residue was dissolved in ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel and eluted with (hexane : ethyl acetate = 9:1) to give 2-hydroxy-4-octyloxybenzaldehyde (6.73 g).

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=8.8Hz), 1.2-1.5 (10H, m), 1.8-2.0 (2H, m), 4.0-4.2 (2H, m), 6.42 (1H, s), 6.52 (1H, d, J=8.7Hz), 7.79 (1H, d, J=8.7Hz), 10.33 (1H, s)

APCI-MASS : e/z = 257 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 4 (1).

Preparation 4 (2)

Methyl 3,4-dipentyloxybenzoate

NMR ($CDCl_3$, δ) : 0.93 (6H, t, J=6.0 and 9.0Hz), 1.3-2.0 (12H, m), 3.88 (3H, s), 4.04 (4H, m), 6.86(1H, d, J=8.4Hz), 7.53 (1H, d, J=2.0Hz), 7.63(1H, dd, J=8.4 and 2.0Hz)

APCI-MASS : e/z = 309 (M^++1)

Preparation 5 (1)

A mixture of 4-bromo-4'-pentylbiphenyl (5.04 g), trimethylsilylacetylene (2.4 ml), tetrakis(triphenylphosphine)palladium (0.96 g), triphenylphosphine (0.22 g) and cuprous iodide (95 mg) in piperidine (10 ml) was heated for an hour under atmospheric pressure of nitrogen at 90°C. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and adjusted to about pH 1 with 6N hydrochloric acid. The separated organic layer was washed with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give crude 2-[4-(4-pentylphenyl)phenyl]-1-trimethylsilylacetylene, which was used for the next reaction without further purification. Crude mixture was dissolved in a mixture of dichloromethane (10 ml) and methanol (10 ml), and to the solution was added potassium carbonate (2.75 g) at 0°C.

The mixture was allowed to warm to ambient temperature, and stirred for another 2 hours. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and the resultant precipitate was filtered off. The filtrate was adjusted to about pH 7 with 1N hydrochloric acid, and washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude powder, which was subjected to column chromatography on silica gel (300 ml), and eluted with a mixture of (n-hexane : ethyl acetate = 99:1 - 97:3, V/V) to give 4-(4-pentylphenyl)phenylacetylene (2.09g).

IR (Nujol) : 3274, 1490 cm^{-1}

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.4Hz), 1.30-1.50 (4H, m), 1.50-1.80 (2H, m), 2.64 (2H, t, J=7.6Hz), 7.20-7.30 (2H, m), 7.45-7.60 (6H, m)

APCI-MASS : e/z = 281 (M^++1 + MeOH)

The following compound was obtained according to a similar manner to that of Preparation 5 (1).

Preparation 5 (2)

6-heptyloxynaphthalen-2-yl-acetylene

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.60 (8H, m), 1.70-1.90 (2H, m), 3.10 (1H, s), 4.07 (2H, t, J=6.5Hz), 7.08 (1H, d, J=2.5Hz), 7.15 (1H, dd, J=2.5 and 8.9Hz), 7.47 (1H, dd, J=1.6 and 8.5Hz), 7.64 (1H, d, J=7.3Hz), 7.68 (1H, d, J=8.5Hz), 7.94 (1H, d, J=1.6Hz)

APCI-MASS : e/z = 267 (M^++1)

Preparation 6 (1)

To a solution of 4-(4-pentylphenyl)phenylacetylene (2.09 g) in tetrahydrofuran (30 ml) was added dropwise a solution of lithium diisobutylamide in a mixture of

tetrahydrofuran and n-hexane (1.60 M, 5.6 ml) at -75°C, and the resultant mixture was stirred for an hour at -78°C. To the mixture was added methyl chloroformate (0.72 ml), and the reaction mixture was allowed to warm to ambient temperature. The solution was diluted with ethyl acetate, and washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude product, which was subjected to column chromatography on silica gel (150 ml), and eluted with a mixture of (n-hexane : ethyl acetate = 100:0 - 9:1, V/V) to give methyl 3-[4-(4-pentylphenyl)phenyl]propionate (2.20 g).

IR (Nujol) : 2225, 1712 cm^{-1}

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.25-1.50 (4H, m), 1.52-1.80 (2H, m), 2.64 (2H, t, J=7.6Hz), 3.85 (3H, s), 7.20-7.35 (2H, m), 7.40-7.70 (6H, m)

APCI-MASS : e/z = 307 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 6 (1).

Preparation 6 (2)

Methyl 3-(6-heptyloxynaphthalen-2-yl)propionate

IR (Nujol) : 2219, 1704, 1621 cm^{-1}

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.60 (8H, m), 1.70-2.00 (2H, m), 3.86 (3H, s), 4.08 (2H, t, J=6.5Hz), 7.10 (1H, d, J=2.5Hz), 7.17 (1H, dd, J=2.5 and 8.9Hz), 7.52 (1H, dd, J=1.6 and 8.5Hz), 7.68 (1H, d, J=7.3Hz), 7.72 (1H, d, J=8.5Hz), 8.06 (1H, d, J=1.6Hz)

APCI-MASS : e/z = 325 (M^++1)

Preparation 7 (1)

A mixture of 4-bromo-4'-pentylbiphenyl (5.0 g), methyl acrylate (2.2 ml), palladium acetate (0.11 g) and tris(o-tolyl)phosphine (0.60 g) in triethylamine (16 ml) was refluxed for 15 hours under nitrogen atmosphere. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and adjusted to about pH 1.5 with 6N hydrochloric acid. The separated organic layer was washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give a crude powder, which was subjected to column chromatography on silica gel (200 ml), and eluted with a mixture of (n-hexane : ethyl acetate = 100:0 - 94:6, V/V) to give methyl 3-[4-(4-pentylphenyl)phenyl]-acrylate (4.48 g).

IR (Nujol) : 1718, 1637 cm^{-1}

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=6.7Hz), 1.20-1.50 (4H, m), 1.50-1.80 (2H, m), 2.65 (2H, t, J=7.4Hz), 3.82 (3H, s), 6.47 (1H, d, J=16.0Hz), 7.20-7.35 (2H, m), 7.45-7.68 (6H, m), 7.73 (1H, d, J=16.0Hz)

APCI-MASS : e/z = 309 (M^++1)

The following compounds [Preparations 7 (2) to (4)] were obtained according to a similar manner to that of Preparation 7 (1).

Preparation 7 (2)

Methyl 3-(6-heptyloxynaphthalen-2-yl)acrylate

IR (Nujol) : 1716, 1625, 1459 cm^{-1}

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.65 (8H, m), 1.76-1.93 (2H, m), 3.82 (3H, s), 4.07 (2H, t, J=6.5Hz), 6.49 (1H, d, J=16.0Hz), 7.05-7.20 (2H, m), 7.55-7.90 (5H, m)

APCI-MS : e/z = 327 (M^++1)

Preparation 7 (3)

Methyl 3-[4-(4-heptylphenyl)phenyl]acrylate

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=6.5Hz), 1.15-1.50 (8H, m), 1.50-1.75 (2H, m), 2.64 (2H, t, J=7.6Hz), 3.81 (3H, s), 6.46 (1H, d, J=16.0Hz), 7.26 (2H, d, J=8.2Hz), 7.52 (2H, d, J=8.2Hz), 7.59 (6H, s), 7.73 (1H, d, J=16.0Hz)

APCI-MASS : e/z = 337 (M^++1)

Preparation 7 (4)

Methyl 3-[4-(4-pentyloxyphenyl)phenyl]acrylate

NMR ($CDCl_3$, δ) : 0.94 (3H, t, J=7.0Hz), 1.30-1.60 (4H, m), 1.70-1.93 (2H, m), 3.82 (3H, s), 4.00 (2H, t, J=6.7Hz), 6.45 (1H, d, J=16.0Hz), 6.90-7.05 (2H, m), 7.48-8.65 (6H, m), 7.72 (1H, d, J=16.0Hz)

APCI-MASS : e/z = 325 (M^++1)

Preparation 8

A mixture of 6-heptyloxynaphthalen-2-carboxylic acid (1.00 g) and thionyl chloride (5 ml) was stirredn for 18 hours at ambient temparature, and concentrated under reduced pressure to give crude 6-heptyloxy-2-naphthoyl chloride. To a mixture of ethyl isonipecotinate (605 mg), triethylamine (425 mg) and N,N-dimethylaminopyridine (10 mg) in dichloromethane (10 ml) was added crude 6-heptyloxy-2-naphthoyl chloride, and the mixture was stirred for 2 hours at ambient temperature, and diluted with dichloromethane. The mixture was washed with water, 1N hydrochloric acid and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel, and eluted with (n-hexane : ethyl acetate = 3:1) to give 4-ethoxycarbonyl-1-(6-heptyloxy-2-

naphthoyl)piperidine (1.20 g).

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.6Hz), 1.2-2.0 (19H, m), 2.5-2.7 (1H, m), 3.0-3.2 (2H, m), 4.1-4.3 (4H, m), 7.1-7.2 (2H, m), 7.44 (1H, dd, J=8.4 and 1.7Hz), 7.72 (1H, d, J=3.9Hz), 7.77 (1H, d, J=3.9Hz), 7.82 (1H, s)

APCI-MASS : e/z = 426 (M^++1)

Preparation 9

To a mixture of methyl 3,4-diaminobenzoate (1.91 g) and triethylamine (0.56 g) in N,N-dimethylformamide (20 ml) was added decanoyl chloride (2.31 g), and the mixture was stirred for an hour at 0°C. The reaction mixture was diluted with ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. The residue was dissolved in methanol (20 ml), and conc. sulfuric acid (0.05 ml) was added, and the mixture was stirred for 6 hours at 60°C. After cooling, the reaction mixture was evaporated under reduced pressure. The residue was diluted with ethyl acetate, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel eluted with (n-hexane : ethyl acetate = 3:1) gave 5-methoxycarbonyl-2-nonylbenzimidazole (1.40 g).

IR (KBr pelet) : 2923, 1718, 1623, 1544, 1438, 1413, 1288, 1213, 1085, 750 cm^{-1}

NMR (DMSO-d_6, δ) : 0.84 (3H, t, J=6.7Hz), 1.1-1.4 (12H, m), 1.7-1.9 (2H, m), 2.83 (2H, t, J=7.4Hz), 7.56 (1H, d, J=8.4Hz), 7.78 (1H, d, J=8.4Hz), 8.07 (1H, s)

APCI-MASS : e/z = 303 (M^++1)

Preparation 10

To a mixture of dimethylmalonate (4 ml), 2-hydroxy-4-octyloxybenzaldehyde (2.50 g) and piperidine (0.1 ml) in methanol (10 ml) was added acetic acid (0.01 ml), and the mixture was stirred for 3 hours at 70°C. The solvents were removed under reduced pressure, and the residue was dissolved in ethyl acetate, and washed with 0.5N hydrochloric acid, water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and filtrate was evaporated under reduced pressure, and the precipitate was collected by filtration, and washed with n-hexane, and dried to give methyl 7-octyloxycoumarin-3-carboxylate (0.94 g).

NMR (DMSO-d_6, δ) : 0.86 (3H, m), 1.2-1.6 (10H, m), 1.7-1.8 (2H, m), 3.81 (3H, s), 4.11 (2H, t, J=6.4Hz), 6.9-7.1 (2H, m), 7.83 (1H, d, J=9.0Hz), 8.75 (1H, s)

APCI-MASS : e/z = 333 (M^++1)

Preparation 11

To a mixture of sodium hydride (423 mg) and 4-octylphenol (2.06 g) in tetrahydrofuran (16 ml) was added dropwise ethyl 2-chloroacetoacetate at ambient temperature. The mixture was stirred for 6 hours at 70°C under nitrogen atmosphere, and poured into saturated ammonium chloride aqueous solution. The solution was extracted with ethyl acetate, and the organic layer was washed with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was added to conc. H_2SO_4 (10 ml) at 0°C, and mixture was stirred for 10 minutes. The reaction mixture was poured into ice-water, and adjusted to pH 7.0 with 1N

NaOH aqueous solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column-chromatography on silica gel, and eluted with (hexane : ethyl acetate = 95:5). The fractions containing the object compound were combined, and evaporated under reduced pressure to give ethyl 3-methyl 5-octylbenzo[b]furan-2-carboxylate (1.44 g).

IR (Neat) : 2925, 2854, 1712, 1596, 1463, 1292, 1149, 1089 cm^{-1}

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=6.7Hz), 1.2-1.5 (10H, m), 1.44 (3H, t, J=7.1Hz), 1.6-1.8 (2H, m), 2.58 (3H, s), 2.71 (2H, t, J=8.0Hz), 4.45 (2H, t, J=7.1Hz), 7.2-7.5 (3H, m)

APCI-MASS : e/z = 317 (M^++1)

Preparation 12

To a solution of ethyl 3-amino-4-hydroxybenzoate (1.81 g) and triethylamine (1.53 ml) in dichloromethane (20 ml) was dropwise added decanoyl chloride (2.01 ml) at 0°C. The reaction mixture was stirred for 48 hours at ambient temperature, and washed with water, 0.5N hydrochloric acid, water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. To the residue dissolved in xylene (30 ml) was added p-tolune sulfonic acid monohydrate (0.5 g), and the mixture was stirred for 4 hours at 130°C . Ethyl acetate was added to the mixture, and washed with water and brine. The separated organic layer was dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure. Purification of the residue by

column chromatography on silica gel elluted with (n-hexane : ethyl acetate = 9:1, V/V) gave ethyl 2-nonyl benzo[b]oxazole-6-carboxylate (2.36 g).

IR (KBr pelet) : 2914, 1722, 1621, 1575, 1470, 1429, 1365, 1290, 1203, 1151, 1115, 1081, 1022 cm^{-1}

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=6.7Hz), 1.2-1.4 (12H, m), 1.42 (3H, t, J=7.2Hz), 1.90 (2H, m), 2.95 (2H, t, J=7.4Hz), 4.40 (2H, q, J=7.0Hz), 7.50 (1H, d, J=8.5Hz), 8.06 (1H, d, J=8.5Hz), 8.37 (1H, s)

APCI-MASS : e/z = 318 (M^++1)

Preparation 13

A mixture of methyl 3,4-diaminobenzoate (1.84 g) and 4-hexyloxy benzaldehyde (2.30 g) in nitrobenzene (40 ml) was stirred for 48 hours at 145°C. After cooling, the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel eluted with (n-hexane : ethyl acetate = 2:1) gave 5-methoxycarbonyl-2-(4-hexyloxyphenyl)-benzimidazole (1.19 g).

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.4Hz), 1.2-1.9 (8H, m), 3.92 (3H, s), 3.90-4.1 (2H, m), 6.93 (2H, d, J=8.9Hz), 7.5-7.8 (1H, br), 7.94 (1H, dd, J=8.5 and 1.5Hz), 8.03 (1H, d, J=8.9Hz), 8.2-8.4 (1H, br)

APCI-MASS : 353 (M^++1)

Preparation 14

A mixture of methyl 3-[4-(4-pentylphenyl)phenyl]-acrylate (2.0 g) and 10% palladium on carbon (50% wet, 0.2 g) in tetrahydrofuran (20 ml) was stirred for 8 hours under atmospheric pressure of hydrogen at ambient temparature. The catalyst was filtered off, and the

filtrate was evaporated under reduced pressure to give methyl 3-[4-(4-pentylphenyl)phenyl]propionate (1.93 g).

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.8Hz), 1.25-1.50 (4H, m), 1.50-1.75 (2H, m), 2.55-2.75 (4H, m), 2.99 (2H, t, J=8.0Hz), 3.68 (3H, s), 7.10-7.30 (4H, m), 7.40-7.60 (4H, m)

APCI-MASS : e/z = 311 (M^++1)

Preparation 15 (1)

A mixture of methyl 3-[4-(4-pentyloxyphenyl)phenyl]-acrylate (2.70 g) and platinum oxide (0.41 g) in tetrahydrofuran (40 ml) was stirred for 8 hours under 3 atom of hydrogen at ambient temperature. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give methyl 3-[4-(4-pentyloxyphenyl)phenyl]-propionate (2.70 g).

NMR ($CDCl_3$, δ) : 0.94 (3H, t, J=7.0Hz), 1.28-1.60 (4H, m), 1.60-1.95 (2H, m), 2.55-2.78 (2H, m), 2.98 (2H, t, J=7.8Hz), 3.98 (2H, t, J=6.5Hz), 6.85-7.05 (2H, m), 7.05-7.30 (2H, m), 7.40-7.55 (4H, m)

APCI-MASS : e/z = 327 (M^++1)

The following compound was obtained according to a similar manner to that of Preparation 15 (1).

Preparation 15 (2)

Methyl 3-(6-heptyloxynaphthalen-2-yl)propionate

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.70 (8H, m), 1.70-1.93 (2H, m), 2.70 (2H, t, J=7.7Hz), 3.07 (2H, t, J=7.7Hz), 3.67 (3H, s), 4.05 (2H, t, J=6.5Hz), 7.02-7.20 (2H, m), 7.20-7.38 (2H, m), 7.55 (1H, s), 7.66 (1H, dd, J=3.0 and 8.5Hz)

APCI-MASS : e/z = 329 (M^++1)

Preparation 16 (1)

To a mixture of methyl 3-[4-(4-pentylphenyl)phenyl]-acrylate (0.41 g) in tetrahydrofuran (5 ml) was added 3N NaOH aqueous solution (1.3 ml), and the resultant mixture was heated to 85°C for 10 hours. The reaction mixture was poured into a mixture of cold water and ethyl acetate, and adjusted to about pH 2 with 6N hydrochloric acid. The separated organic layer was washed in turn with water and brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 3-[4-(4-pentylphenyl)phenyl]acrylic acid (0.41 g).

NMR ($DMSO-d_6$, δ) : 0.87 (3H, t, J=7.5Hz), 1.15-1.46 (4H, m), 1.48-1.70 (2H, m), 2.61 (2H, t, J=7.4Hz), 6.56 (1H, d, J=16.0Hz), 7.29 (2H, d, J=8.2Hz), 7.60 (2H, d, J=4.0Hz), 7.66 (2H, d, J=4.0Hz), 7.68-7.85 (3H, m)

APCI-MASS : e/z = 295 (M^++1)

The following compounds [Preparations 16 (2) to (9)] were obtained according to a similar manner to that of Preparation 16 (1).

Preparation 16 (2)

3-[4-(4-Pentyloxyphenyl)phenyl]propionic acid

IR (Nujol) : 1697, 1606, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 0.94 (3H, t, J=7.1Hz), 1.25-1.60 (4H, m), 1.70-1.95 (2H, m), 2.72 (2H, t, J=7.5Hz), 3.00 (2H, t, J=7.5Hz), 3.99 (2H, t, J=6.5Hz), 6.95 (2H, dd, J=2.1 and 6.7Hz), 7.25 (2H, d, J=8.2Hz), 7.40-7.60 (4H, m)

APCI-MASS : e/z = 313 (M^++1)

Preparation 16 (3)

3-[4-(4-Heptylphenyl)phenyl]propionic acid

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=6.8Hz), 1.15-1.50 (8H, m), 1.50-1.78 (2H, m), 2.65 (2H, t, J=7.6Hz), 6.48 (1H, d, J=16.0Hz), 7.27 (2H, d, J=8.2Hz), 7.53 (2H, d, J=8.2Hz), 7.63 (4H, m), 7.83 (1H, d, J=16.0Hz)

APCI-MASS : e/z = 323 (M^++1)

Preparation 16 (4)

3-[4-(4-Pentylphenyl)phenyl]propionic acid

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.4Hz), 1.20-1.50 (4H, m), 1.50-1.75 (2H, m), 2.64 (2H, t, J=8.0Hz), 2.67 (2H, t, J=9.6Hz), 3.00 (2H, t, J=8.0Hz), 7.15-7.38 (4H, m), 7.38-7.60 (4H, m)

APCI-MASS : e/z = 297 (M^++1)

Preparation 16 (5)

3-(6-Heptyloxynaphthalen-2-yl)propionic acid

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.65 (8H, m), 1.75-2.00 (2H, m), 2.75 (2H, t, J=7.7Hz), 3.09 (2H, t, J=7.7Hz), 4.06 (2H, t, J=6.5Hz), 7.05-7.15 (2H, m), 7.15-7.35 (2H, m), 7.50-7.73 (2H, m)

APCI-MASS : e/z = 315 (M^++1)

Preparation 16 (6)

3-(6-Heptyloxynaphthalen-2-yl)acrylic acid

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.15-1.60 (8H, m), 1.75-1.95 (2H, m), 4.09 (2H, t, J=6.5Hz), 6.51 (1H, d, J=16.0Hz), 7.09-7.30 (2H, m), 7.65-8.00 (5H, m)

Preparation 16 (7)

3-[4-(4-Pentylphenyl)phenyl]propionic acid

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=6.5Hz), 1.23-1.50 (4H, m), 1.50-1.80 (2H, m), 2.65 (2H, t,

J=7.6Hz), 7.27 (2H, d, J=8.2Hz), 7.51 (2H, d, J=8.2Hz), 7.58-7.80 (4H, m)

APCI-MASS : e/z = 325 (M^++1 + MeOH)

Preparation 16 (8)

3-(6-Heptyloxynaphthalen-2-yl)propionic acid

IR (Nujol) : 2645, 2198, 1670, 1627 cm^{-1}

NMR (DMSO-d_6, δ) : 0.85 (3H, t, J=6.5Hz), 1.10-1.60 (8H, m), 1.65-1.90 (2H, m), 4.10 (2H, t, J=6.5Hz), 7.24 (1H, dd, J=2.4 and 8.9Hz), 7.39 (1H, d, J=2.5Hz), 7.55 (1H, dd, J=1.6 and 8.5Hz), 7.8-8.0 (2H, m), 8.22 (1H, d, J=1.6Hz)

APCI-MASS : e/z = 343 (M^++1 + MeOH)

Preparation 16 (9)

4-[5-(4-Pentyloxyphenyl)isoxazolyl-3-yl]benzoic acid

IR (KBr) : 2939, 2867, 1681, 1614, 1429, 1255, 1178, 821 cm^{-1}

NMR (DMSO-d_6, δ) : 0.91 (3H, t, J=7.1Hz), 1.3-1.5 (4H, m), 1.6-1.8 (2H, m), 4.04 (2H, t, J=6.5Hz), 7.11 (2H, d, J=8.9Hz), 7.54 (1H, s), 7.85 (2H, d, J=8.9Hz), 7.98 (2H, d, J=8.6Hz), 8.11 (2H, d, J=8.6Hz)

APCI-MASS : 352 $(M+H)^+$

Preparation 17 (1)

To a solution of ethyl 3-methyl 5-octylbenzo[b]furan-2-carboxylate (1.44 g) in ethanol (20 ml) was added 10% NaOH aqueous solution (2.2 ml), and stirred for 2 hours at ambient temperature, and evaporated under reduced pressure. The residue was adjusted to pH 3.0 with 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to

give 3-methyl-5-octylbenzo[b]furan-2-carboxylic acid (1.00 g).

IR (KBr pelet) : 2923, 1689, 1664, 1581, 1456, 1319, 1159, 933 cm^{-1}

NMR (DMSO-d_6, δ) : 0.85 (3H, t, J=6.7Hz), 1.2-1.5 (10H, m), 1.5-1.8 (2H, m), 2.49 (3H, s), 2.69 (2H, t, J=7.9Hz), 7.32 (1H, dd, J=8.5 and 1.7Hz), 7.52 (1H, d, J=8.5Hz), 7.54 (1H, d, J=1.7Hz), 13.2-13.5 (1H, br)

APCI-MASS : e/z = 289 (M^++1)

The following compounds [Preparations 17(2) to (8)] were obtained according to a similar manner to that of Preparation 17 (1).

Preparation 17 (2)

3,4-Dipentyloxybenzoic acid

NMR (DMSO-d_6, δ) : 0.89 (6H, t, J=6.8Hz), 1.2-1.5 (8H, m), 1.6-1.8 (4H, m), 3.9-4.1 (4H, m), 7.02 (1H, d, J=8.4Hz), 7.43 (1H, d, J=1.7Hz), 7.53 (1H, dd, J=8.4 and 1.7Hz)

APCI-MASS : e/z = 295 (M^++1)

Preparation 17 (3)

1-(6-Heptyloxy-2-naphthoyl)piperidine-4-carboxylic acid

NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=6.7Hz), 1.2-2.0 (14H, m), 2.5-2.6 (1H, m), 2.9-3.2 (2H, br), 3.25 (2H, s), 4.09 (2H, t, J=6.5Hz), 7.20 (1H, dd, J=8.9 and 2.4Hz), 7.36 (1H, d, J=2.3Hz), 7.43 (1H, dd, J=8.4 and 1.5Hz), 7.8-8.0 (3H, m), 12.30 (1H, br)

APCI-MASS : e/z = 398 (M^++1)

Preparation 17 (4)

7-Octyloxycoumarin-3-carboxylic acid

IR (KBr) : 1748, 1625, 1558, 1467, 1430, 1386, 1360, 1257, 1217, 1120 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.8Hz), 1.2-1.5 (10H, m), 1.6-1.8 (2H, m), 4.11 (2H, t, J=6.4Hz), 6.9-7.1 (2H, m), 7.82 (1H, d, J=8.9Hz), 8.72 (1H, s), 12.98 (1H, br)

APCI-MASS : e/z = 319 (M^++1)

Preparation 17 (5)

4-(4-Pentyloxyphenyl)cinnamic acid

IR (Nujol) : 2923, 1675, 1500, 1290, 1223, 985, 821 cm^{-1}

NMR (DMSO-d_6, δ) : 0.90 (3H, t, J=7.0Hz), 1.3-1.5 (4H, m), 1.6-1.8 (2H, m), 4.01 (2H, t, J=6.5Hz), 6.54 (1H, d, J=16.0Hz), 7.02 (2H, d, J=8.8Hz), 7.5-7.8 (7H, m)

APCI-MASS : e/z = 311 (M^++1)

Preparation 17 (6)

2-Nonylbenzoxazole-6-carboxylic acid

NMR (DMSO-d_6, δ) : 0.84 (3H, t, J=6.7Hz), 1.2-1.5 (12H, m), 1.7-1.9 (2H, m), 2.96 (2H, t, J=7.4Hz), 7.76 (1H, d, J=8.4Hz), 7.98 (1H, d, J=8.4Hz), 8.19 (1H, s)

APCI-MASS : e/z = 290 (M^++1)

Preparation 17 (7)

2-(4-Hexyloxyphenyl)benzimidazole-5-carboxylic acid

NMR (DMSO-d_6, δ) : 0.8-1.0 (3H, m), 1.3-1.6 (6H, m), 1.7-1.8 (2H, m), 4.06 (2H, t, J=6.4Hz), 7.12 (2H, d, J=8.8Hz), 7.6-7.9 (2H, m), 8.1-8.2 (3H, m), 13.00 (1H, br)

APCI-MASS : e/z = 339 (M^++1)

Preparation 17 (8)

2-Nonylbenzimidazole-5-carboxylic acid

NMR (DMSO-d_6, δ) : 0.85 (3H, t, J=6.7Hz), 1.1-1.4 (12H, m), 2.7-2.9 (2H, m), 2.96 (2H, t, J=7.6Hz), 3.6-5.2 (1H, br), 7.66 (1H, d, J=8.4Hz), 7.90 (1H, d, J=8.4Hz), 8.15 (1H, s)

APCI-MASS : e/z = 289 (M^++1)

Preparation 18

A solution of 4-[4-(4-octyloxyphenyl)piperazin-1-yl]benzonitrile (0.5 g) in 20% H_2SO_4 aqueous solution (30 ml) and acetic acid (20 ml) was refluxed for 9 hours. The reaction mixture was pulverized with water. The precipitate was collected by filtration, and added to a mixture of water, tetrahydrofuran and ethyl acetate, and adjusted to pH 2.5 with 1N NaOH aqueous solution. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-(4-octyloxyphenyl)piperazin-1-yl]benzoic acid (388 mg).

IR (KBr) : 2929, 1664, 1600, 1510, 1240 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.6Hz), 1.2-1.5 (10H, m), 1.5-1.8 (2H, m), 3.13 (4H, t, J=5.3Hz), 3.44 (4H, t, J=5.3Hz), 3.88 (2H, t, J=6.5Hz), 6.83 (2H, d, J=9.2Hz), 6.94 (2H, d, J=9.2Hz), 7.02 (2H, d, J=9.0Hz), 7.79 (2H, d, J=9.0Hz)

APCI-MASS : e/z = 411 (M^++1)

Preparation 19

To a suspension of sodium hydride (60% suspension in mineral oil) (0.296 g) in N,N-dimethylformamide (14 ml) was added 1,2,4-triazole (0.511 g) and 4-[4-(8-bromooctyloxy)phenyl]benzoic acid (1 g), and was stirred for 5 hours at 120°C. The reaction mixture was added to a

mixture of water and ethyl acetate, and adjusted to pH 2.5 with conc. hydrochloric acid. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-[8-(1,2,4-triazol-1-yl)octyloxy]phenyl]benzoic acid (0.81 g).

IR (KBr) : 2940, 1689, 1604, 1297, 1189 cm^{-1}

NMR (DMSO-d_6, δ) : 1.1-1.53 (8H, m), 1.6-1.9 (4H, m), 4.00 (2H, t, J=6.3Hz), 4.16 (2H, t, J=7.0Hz), 7.03 (2H, d, J=8.7Hz), 7.67 (2H, d, J=8.7Hz), 7.75 (2H, d, J=8.4Hz), 7.95 (1H, s), 7.99 (2H, d, J=8.4Hz), 8.51 (1H, s), 12.9 (1H, s)

APCI-MASS : e/z = 394 (M^++1)

Preparation 20

A mixture of 2-carbamoyl-5-methoxybenzo[b]thiophene (2.0 g), acetic acid (5 ml) and 48% hydrobromic acid (20 ml) was stirred for 16 hours at 110°C, and the mixture was poured into the ice-water. The resulting precipitate was collected by filtration, and dried to give 5-hydroxybenzo[b]thiophene-2-carboxylic acid (1.66 g).

NMR (DMSO-d_6, δ) : 7.03 (1H, dd, J=8.8 and 0.6Hz), 7.31 (1H, d, J=0.6Hz), 7.81 (1H, d, J=8.8Hz), 7.96 (1H, s), 9.64 (1H, s), 13.32 (1H, s)

APCI-MASS : e/z = 195 (M^++1)

Preparation 21 (1)

A solution of (S)-2-tert-butoxycarbonyl-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (1 g) in a mixture of 10% NaOH aqueous solution (2.73 ml) and dimethylsulfoxide (11 ml) was stirred for half an hour at 80°C. Then, octyl bromide (0.589 ml) was added thereto, and stirred for 4 hours at 60°C. The reaction mixture was added to a mixture of water and ethyl acetate, and

adjusted to pH 2.5 with conc. hydrochloric acid. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give (S)-2-tert-butoxycarbonyl-1,2,3,4-tetrahydro-7-octyloxyisoquinoline-3-carboxylic acid (1.30 g).

IR (Neat) : 2929, 1743, 1704, 1164 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.1Hz), 1.1-1.6 (10H, m), 1.41 + 1.51 (9H, s, cis + trans), 1.75 (2H, quint, J=6.5Hz), 3.10 (2H, m), 3.90 (2H, t, J=3.9Hz), 4.42 (1H, d, J=16.8Hz), 4.65 (1H, d, J=16.8Hz), 4.74 + 5.09 (1H, m, cis + trans), 6.5-6.8 (2H, m), 7.03 (1H, d, J=8.3Hz)

APCI-MASS : e/z = 306 $(M^+ + 1)$-Boc

The following compounds [Preparations 21 (2) to (3)] were obtained according to a similar manner to that of Preparation 21 (1).

Preparation 21 (2)

5-Octyloxybenzo[b]thiophene-2-carboxylic acid

IR (KBr) : 1673, 1666, 1600, 1517, 1409, 1267, 1214, 1153, 865 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 1.2-1.5 (10H, m), 1.7-1.9 (2H, m), 4.02 (2H, t, J=6.4Hz), 7.13 (1H, dd, J=8.9 and 0.6Hz), 7.51 (1H, d, J=0.6Hz), 7.90 (1H, d, J=9.0Hz), 7.99 (1H, s)

APCI-MASS : e/z = 307 $(M^+ + 1)$

Preparation 21 (3)

4-[4-(4-Hexyloxyphenyl)piperazin-1-yl]benzoic acid dihydrochloride

IR (KBr) : 1668, 1600, 1510, 1228 cm^{-1}

NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=6.9Hz), 1.2-1.5

(6H, m), 1.6-1.9 (2H, m), 3.0-3.2 (4H, m), 3.3-3.5 (4H, m), 3.88 (2H, t, J=6.3Hz), 6.83 (2H, d, J=9Hz), 6.9-7.1 (4H, m), 7.79 (2H, d, J=8.8Hz), 12.32 (1H, s)

APCI-MASS : e/z = 383 ($M+H^+$)

Preparation 22

To a suspension of dimethyl terephthalate (1.94 g) and potassium t-butoxide (2.24 g) in tetrahydrofuran (30 ml) was added 4-pentyloxyacetophenone (1.59 g) in tetrahydrofuran (10 ml) at 70°C dropwise. The mixture was refluxed for 30 minutes and poured into 1N HCl (50 ml). The mixture was extracted with ethyl acetate (100 ml) and the organic layer was washed with H_2O (100 ml), brine (100 ml) and evaporated under reduced pressure. The residue was triturated with acetonitrile (20 ml), collected by filtration and dried under reduced pressure to give 1-(4-methoxycarbonylphenyl)-3-(4-pentyloxyphenyl)propane-1,3-dione (2.41 g) as yellow solid.

IR (KBr) : 3475, 2956, 2923, 1720, 1606, 1508, 1284, 1176, 1108, 769 cm^{-1}

NMR ($CDCl_3$, δ) : 0.95 (3H, t, J=7.0Hz), 1.3-1.5 (4H, m), 1.7-2.0 (2H, m), 3.96 (3H, s), 4.04 (2H, t, J=6.5Hz), 6.82 (1H, s), 6.96 (2H, d, J=8.9Hz), 8.0-8.1 (4H, m), 8.14 (2H, m, J=8.7Hz), 12-13 (1H, br)

APCI-MASS : 369 ($M+H^+$)

Preparation 23

The solution of 1-(4-methoxycarbonylphenyl)-3-(4-pentyloxyphenyl)propane-1,3-dione (1.00 g) and hydroxylamine hydrochloride (567 mg) in methanol (10 ml) was refluxed for 10 hours. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (50 ml x 2), brine (50 ml). The organic layer was dried

over magnesium sulfate and the solvents were removed under reduced pressure. The residue was triturated with acetonitrile (10 ml), collected by filtration, and dried under reduced pressure to give methyl 4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoate (0.74 g).

IR (KBr) : 2942, 2873, 1716, 1616, 1508, 1280, 1108 cm^{-1}

NMR ($CDCl_3$, δ) : 0.95 (3H, t, J=6.9Hz), 1.3-1.6 (4H, m), 1.8-2.0 (2H, m), 3.95 (3H, s), 4.02 (2H, t, J=6.5Hz), 6.74 (1H, s), 6.99 (2H, d, J=8.8Hz), 7.76 (2H, d, J=8.8Hz), 7.93 (2H, d, J=8.5Hz), 8.14 (2H, d, J=8.5Hz)

APCI-MASS : 366 $(M+H)^+$

Preparation 24

A solution of 4-[4-(8-bromooctyloxy)phenyl]benzoic acid (1 g) in a mixture of sodium methylate (28% solution in methanol) (10 ml) and N,N-dimethylformamide (5 ml) was refluxed for 5 hours. The reaction mixture was added to a mixture of water and ethyl acetate and adjusted to pH 2.0 with conc. HCl. The organic layer was taken and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-[4-(8-methoxyoctyloxy)phenyl]-benzoic acid (0.77 g).

IR (KBr) : 2935, 1685, 835, 773 cm^{-1}

NMR ($CDCl_3$, δ) : 1.27-1.7 (10H, m), 1.7-1.95 (2H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4Hz), 4.01 (2H, t, J=6.5Hz), 6.99 (2H, d, J=8.7Hz), 7.58 (2H, d, J=8.7Hz), 7.66 (2H, d, J=8.4Hz), 8.15 (2H, d, J=8.4Hz)

APCI-MASS : e/z = 339 $(M^+ + H - H_2O)$

Preparation 25 (1)

To a suspension of 1-hydroxybenzotriazole (0.283 g)

and 6-octyloxymethylpicolinic acid (0.505 g) in dichloromethane (15 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (0.473 g), and stirred for 3 hours at ambient temperature. The reaction mixture was poured into water. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-(6-octyloxymethylpicolinoyl)benzotriazole 3-oxide (737 mg).

IR (Neat) : 1793, 1654, 1591, 1039 cm^{-1}

The following compounds [Preparations 25 (2) to (18)] were obtained according to a similar manner to that of Preparation 25 (1).

Preparation 25 (2)

1-[4-(4-Octyloxyphenyl)piperazin-1-yl)benzoyl]-benzotriazole 3-oxide

IR (KBr) : 1783, 1600, 1511, 1232, 1184 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.6Hz), 1.2-1.65 (10H, m), 1.65-1.9 (2H, m), 3.24 (4H, t, J=5.3Hz), 3.62 (4H, t, J=5.3Hz), 3.93 (2H, t, J=6.5Hz), 6.8-7.1 (6H, m), 7.35-7.63 (3H, m), 8.0-8.25 (3H, m)

Preparation 25 (3)

1-[4-[4-[8-(1,2,4-Triazol-1-yl)octyloxy]phenyl]-benzoyl]benzotriazole 3-oxide

IR (KBr) : 1776, 1600, 1193, 983 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-2.0 (12H, m), 4.03 (2H, t, J=6.4Hz), 4.18 (2H, t, J=7.1Hz), 7.02 (2H, d, J=8.7Hz), 7.4-7.63 (3H, m), 7.63 (2H, d, J=8.7Hz), 7.79 (2H, d, J=8.3Hz), 7.95 (1H, s), 8.06 (1H, s), 8.12 (1H, d, J=7.7Hz), 8.32 (2H, d, J=8.3Hz)

APCI-MASS : e/z = 511 (M^++1)

Preparation 25 (4)

1-[2-Methyl-2-(4-octyloxyphenoxy)propionyl]-benzotriazole 3-oxide

IR (Neat) : 2927, 1810, 1504, 1047 cm^{-1}

Preparation 25 (5)

1-[2-(4-Octyloxyphenoxy)propionyl]benzotriazole 3-oxide

IR (KBr) : 2954, 1812, 1513, 1232 cm^{-1}

Preparation 25 (6)

1-[(S)-2-tert-Butoxycarbonyl-1,2,3,4-tetrahydro-7-octyloxyisoquinolin-3-ylcarbonyl]benzotriazole 3-oxide

IR (Neat) : 2929, 1816, 1739, 1704, 1392 cm^{-1}

Preparation 25 (7)

Succinimido 4-(4-n-octyloxyphenyl)piperazine-1-carboxylate

IR (KBr) : 2925, 1758, 1743, 1513, 1241 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.8Hz), 1.2-1.5 (10H, m), 1.65-1.85 (2H, m), 2.83 (4H, s), 3.0-3.2 (2H, m), 3.6-3.85 (2H, m), 3.91 (2H, t, J=6.5Hz), 6.84 (2H, dd, J=8.5 and 2.7Hz), 6.90 (2H, dd, J=8.5 and 2.7Hz)

APCI-MASS : e/z = 432 (M^++1)

Preparation 25 (8)

(6-Heptyloxy-2-naphthyl)methylsuccinimido carbonate

IR (KBr) : 1878, 1832, 1787, 1735, 1209 cm^{-1}

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.2Hz), 1.2-1.6 (8H, m), 1.73-2.0 (2H, m), 2.83 (4H, s), 4.07 (2H, t, J=6.5Hz), 5.44 (2H, s), 7.13 (1H, d, J=2.4Hz), 7.17 (1H, dd, J=8.8 and 2.4Hz), 7.44 (1H, dd,

J=8.4 and 1.6Hz), 7.67-7.85 (3H, m)

Preparation 25 (9)

1-(3,4-Dipentyloxybenzoyl)benzotriazole 3-oxide

IR (KBr) : 2952, 1774, 1594, 1515, 1430, 1272, 1147, 1089 cm^{-1}

NMR ($CDCl_3$, δ) : 0.9-1.1 (6H, m), 1.3-1.6 (8H, m), 1.8-2.1 (4H, m), 4.0-4.2 (4H, m), 6.99 (1H, d, J=8.5Hz), 7.4-7.6 (3H, m), 7.68 (1H, d, J=2.0Hz), 7.92 (1H, dd, J=8.5 and 2.0Hz), 8.10 (1H, d, J=8.5Hz)

APCI-MASS : e/z = 412 (M^++1)

Preparation 25 (10)

1-(7-Octyloxycoumarin-3-yl-carbonyl)benzotriazole 3-oxide

IR (KBr) : 2925, 1754, 1716, 1610, 1548, 1282, 1199, 1172, 1139, 1064, 781, 750 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=7.8Hz), 1.2-1.5 (10H, m), 1.6-1.8 (2H, m), 4.11 (2H, t, J=6.5Hz), 6.9-7.1 (2H, m), 7.41 (1H, t, J=7.2Hz), 7.54 (1H, t, J=7.2Hz), 7.72 (1H, d, J=8.3Hz), 7.82 (1H, d, J=8.3Hz), 7.99 (1H, d, J=8.3Hz), 8.72 (1H, s)

APCI-MASS : e/z = 436 (M^++1)

Preparation 25 (11)

1-[4-(4-Pentyloxyphenyl)cinnamoyl]benzotriazole 3-oxide

IR (Nujol) : 2854, 1778, 1708, 1620, 1597, 1494, 1459, 1434, 1377, 1350, 1250, 1188, 1138, 1086, 978 cm^{-1}

Preparation 25 (12)

1-(5-Octyloxybenzo[b]thiophen-2-ylcarbonyl)-

benzotriazole 3-oxide

IR (KBr) : 2950, 1776, 1517, 1342, 1211, 1151 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 1.2-1.5 (10H, m), 1.7-1.9 (2H, m), 4.01 (2H, t, J=6.4Hz), 7.13 (1H, dd, J=8.8 and 2.4Hz), 7.42 (1H, d, J=7.1Hz), 7.5-7.6 (3H, m), 7.72 (1H, d, J=8.4Hz), 7.89 (1H, d, J=8.8Hz), 7.9-8.1 (2H, m)

APCI-MASS : e/z = 424 (M^++1)

Preparation 25 (13)

1-(3-Methyl-5-octylbenzo[b]furan-2-yl-carbonyl)-benzotriazole 3-oxide

IR (KBr) : 1776, 1575, 1469, 1363, 1324, 1276, 1114, 1027 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.7Hz), 1.2-1.5 (10H, m), 2.6-2.8 (2H, m), 2.71 (3H, s), 2.76 (2H, t, J=7.4Hz), 7.4-7.6 (6H, m), 8.12 (1H, s)

APCI-MASS : 406 (M^++1)

Preparation 25 (14)

1-(2-Nonylbenzoxazol 5-yl-carbonyl)benzotriazole 3-oxide

IR (KBr) : 2980, 1783, 1623, 1573, 1276, 1151, 1091, 989 cm^{-1}

NMR (DMSO-d_6, δ) : 0.84 (3H, t, J=6.8Hz), 1.1-1.4 (12H, m), 1.81 (2H, t, J=7.2Hz), 2.96 (3H, t, J=7.4Hz), 7.41 (1H, t, J=7.0Hz), 7.54 (1H, t, J=7.0Hz), 7.74 (2H, t, J=7.0Hz), 7.98 (2H, d, J=7.0Hz), 8.19 (1H, s)

APCI-MASS : e/z = 407 (M^++1)

Preparation 25 (15)

1-[2-(4-Hexyloxyphenyl)benzimidazol-5-yl-carbonyl]-benzotriazole 3-oxide

IR (KBr) : 3160, 2931, 2863, 1778, 1612, 1502, 1448,

1388, 1294, 1247, 1174, 1097, 1010, 732 cm^{-1}

NMR (DMSO-d_6, δ) : 0.89 (3H, t, J=6.7Hz), 1.2-1.5 (6H, m), 1.7-1.8 (2H, m), 4.08 (2H, t, J=6.4Hz), 7.16 (2H, d, J=8.7Hz), 7.6-8.4 (9H, m), 8.3-8.6 (1H, br)

APCI-MASS : e/z = 456 (M^++1)

Preparation 25 (16)

1-[4-[4-(8-Methoxyoctyloxy)phenyl]benzoyl]-benzotriazole-3-oxide

IR (KBr) : 2931, 1793, 1770, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 1.2-1.7 (10H, m), 1.7-1.93 (2H, m), 3.34 (3H, s), 3.38 (2H, t, J=6.4Hz), 4.03 (2H, t, J=6.5Hz), 7.03 (2H, d, J=8.8Hz), 7.4-7.7 (3H, m), 7.63 (2H, d, J=8.8Hz), 7.79 (2H, d, J=8.6Hz), 8.12 (1H, d, J=8.2Hz), 8.32 (2H, d, J=8.6Hz)

Preparation 25 (17)

1-[4-[4-(4-Hexyloxyphenyl)piperazin-1-yl]benzoyl]benzotriazole 3-oxide

IR (KBr) : 1770, 1604, 1510, 1232, 1186 cm^{-1}

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=6.6Hz), 1.2-1.6 (6H, m), 1.6-1.9 (2H, m), 3.1-3.3 (4H, m), 3.5-3.7 (4H, m), 3.93 (2H, t, J=6.5Hz), 6.87 (2H, d, J=9.2Hz), 6.96 (2H, d, J=9.2Hz), 7.00 (2H, d, J=9.0Hz), 7.3-7.7 (3H, m), 8.10 (1H, d, J=8.2Hz), 8.15 (2H, d, J=9.0Hz)

APCI-MASS : e/z = 500 ($M+H^+$)

Preparation 25 (18)

1-[4-[5-(4-Pentyloxyphenyl)isoxazol-3-yl]benzoyl]-benzotriazole 3-oxide

IR (KBr) : 2950, 2837, 1774, 1616, 1508, 1452, 1251, 1006 cm^{-1}

NMR ($CDCl_3$, δ) : 0.95 (3H, t, J=7.1Hz), 1.3-1.5 (4H, m), 1.8-2.0 (2H, m), 4.04 (2H, t, J=6.5Hz), 6.81 (1H, s), 7.0-7.1 (3H, m), 7.4-7.6 (3H, m), 7.80 (2H, d, J=8.8Hz), 8.0-8.2 (3H, m), 8.40 (2H, d, J=8.4Hz)

APCI-MASS : 469 $(M+H)^+$

Preparation 26 (1)

To a suspension of 1-hydroxybenzotriazole (0.20 g) and 4-(4-pentylphenyl)cinnamic acid (0.40 g) in dichloromethane (12.0 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (0.33 g) (WSCD·HCl), and the mixture was stirred for 12 hours at ambient temperature. The reaction mixture was diluted with dichloromethane, and washed with brine, and dried over magnesium sulfate. After magnesium sulfate was filtered off, evaporation of the filtrate and trituration with acetonitrile gave 1-[4-(4-pentylphenyl)cinnamoyl]benzotriazole 3-oxide (0.24 g).

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=6.6Hz), 1.20-1.50 (4H, m), 1.50-1.75 (2H, m), 2.66 (2H, t, J=8.0Hz), 7.20-8.25 (11H, m), 8.55 (1H, d, J=8.4Hz)

APCI-MASS : e/z = 412 $(M^+ +1)$

The following compounds [Preparation 26 (2) to (7)] were obtained according to a similar manner to that of Preparation 26 (1).

Preparation 26 (2)

1-[3-[4-(4-Pentyloxyphenyl)phenyl]-2-propanoyl]-benzotriazole 3-oxide

NMR ($CDCl_3$, δ) : 0.90-1.05 (3H, m), 1.30-1.65 (4H, m), 1.70-1.95 (2H, m), 3.10-3.60 (4H, m), 3.90-4.10 (2H, m), 6.88-7.08 (2H, m),

7.20-8.50 (10H, m)

APCI-MASS : e/z = 430 (M^++1)

Preparation 26 (3)

1-[4-(4-Heptylphenyl)cinnamoyl]benzotriazole 3-oxide

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.7Hz), 1.20-1.50 (8H, m), 1.50-1.80 (2H, m), 2.66 (2H, t, J=7.6Hz), 6.70-8.60 (12H, m)

APCI-MASS : e/z = 440 (M^++1)

Preparation 26 (4)

1-[3-[4-(4-Pentylphenyl)phenyl]-2-propanoyl]-benzotriazole 3-oxide

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.8Hz), 1.20-1.50 (4H, m), 1.50-1.76 (2H, m), 2.63 (2H, t, J=7.4Hz), 3.21 (2H, t, J=7.3Hz), 3.51 (2H, t, J=7.3Hz), 7.20-7.45 (4H, m), 7.45-7.70 (5H, m), 7.78 (1H, dt, J=1.0 and 7.2Hz), 8.00 (1H, d, J=8.2Hz), 8.42 (1H, d, J=8.4Hz)

APCI-MASS : e/z = 414 (M^++1)

Preparation 26 (5)

1-[3-(6-Heptyloxynaphthalen-2-yl)propanoyl]-benzotriazole 3-oxide

NMR ($CDCl_3$, δ) : 0.80-1.10 (3H, m), 1.20-1.70 (8H, m), 1.70-2.00 (2H, m), 3.10-3.70 (4H, m), 4.00-4.18 (2H, m), 6.80-8.50 (10H, m)

APCI-MASS : e/z = 432 (M^++1)

Preparation 26 (6)

1-[3-(6-Heptyloxynaphthalen-2-yl)propenoyl]-benzotriazole 3-oxide

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=6.5Hz), 1.20-1.65 (8H, m), 1.75-1.95 (2H, m), 4.10 (2H, d, J=6.5Hz), 6.75-8.62 (8H, m)

APCI-MASS : e/z = 430 (M^++1)

Preparation 26 (7)

1-(4-Hexylphenylbenzoyl)benzotriazole 3-oxide

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=4.4Hz), 1.2-1.5 (6H, m), 1.6-1.8 (2H, m), 2.68 (2H, t, J=8.0Hz), 7.32 (2H, d, J=8.2Hz), 7.4-7.7 (5H, m), 7.81 (2H, d, J=6.6Hz), 8.10 (2H, d, J=8.1Hz), 8.32 (2H, d, J=7.6Hz)

APCI-MASS : e/z = 400 (M^++1)

Preparation 27

To a solution of 4-octyloxyphenol (1 g) in dimethylformamide (10 ml) and pyridine (0.364 ml) was added N,N'-disuccinimidylcarbonate (1.16 g). The mixture was stirred for 12 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 4-octyloxyphenylsuccinimidyl carbonate (0.59 g).

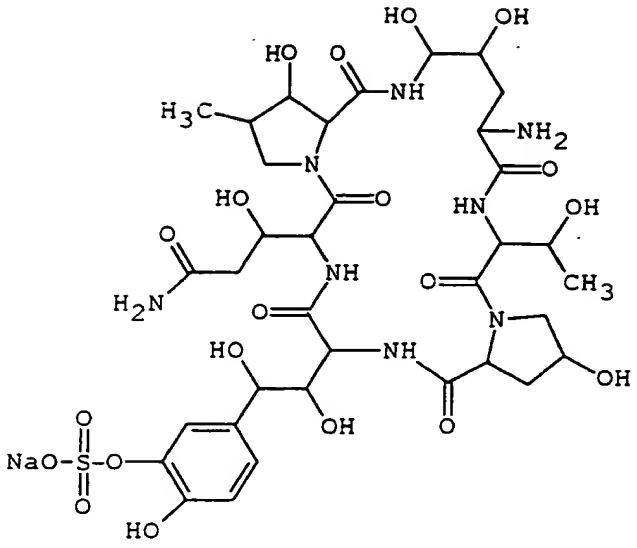
IR (KBr) : 2927, 1876, 1832, 1735 cm^{-1}

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=6.3Hz), 1.2-1.55 (10H, m), 1.67-1.87 (2H, m), 2.87 (4H, s), 3.94 (2H, t, J=6.5Hz), 6.89 (2H, d, J=9.2Hz), 7.17 (2H, d, J=9.2Hz)

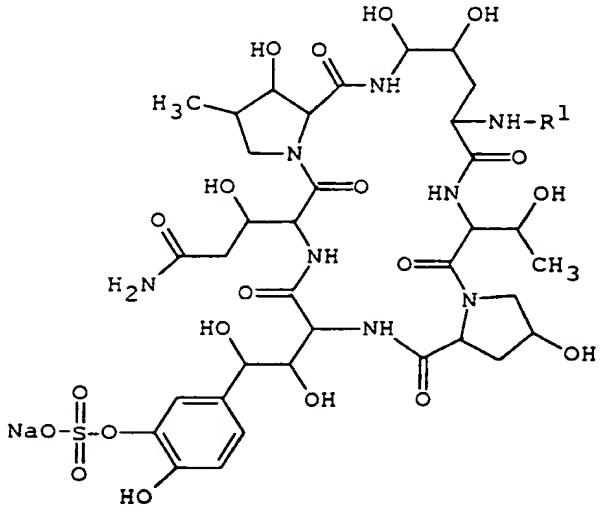
APCI-MASS : e/z = 364 (M^++1)

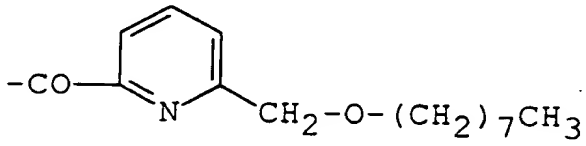
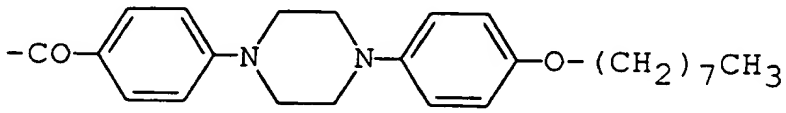
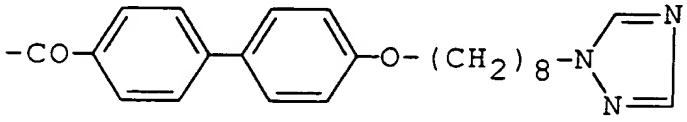
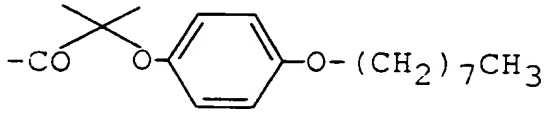
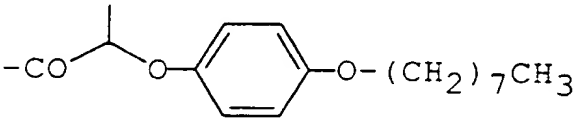
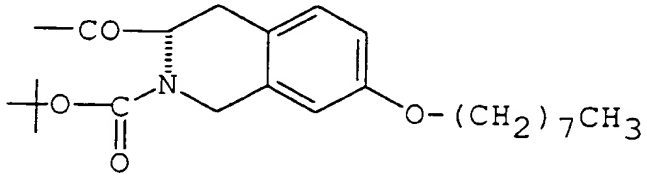
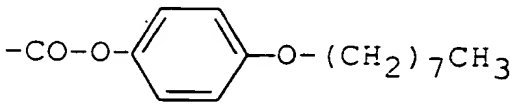
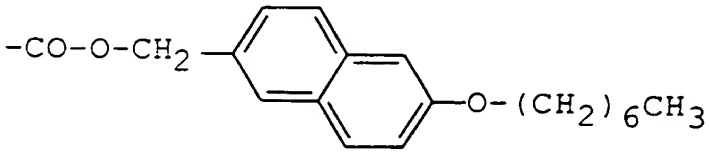
The Starting Compound and the Object Compounds in the following Examples are illustrated by chemical formulae as below.

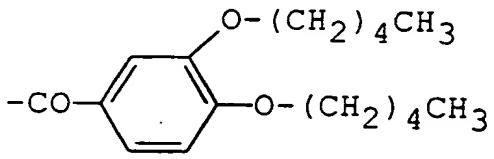
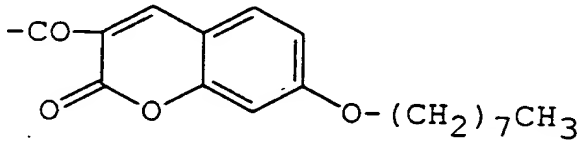
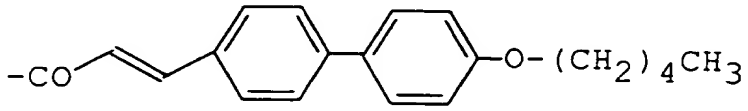
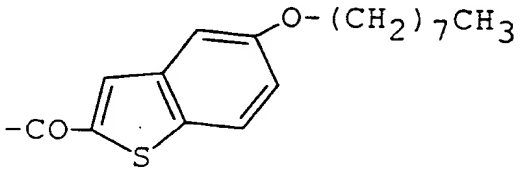
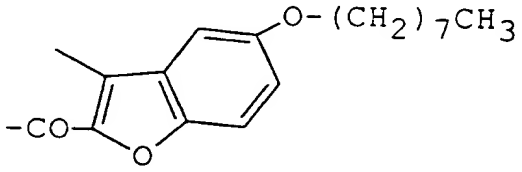
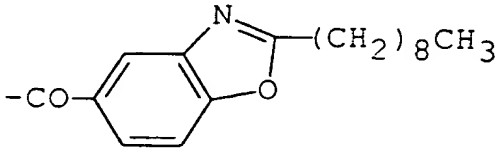
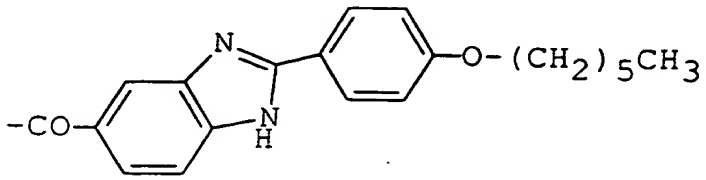
The Starting Compound
(the same in
all Examples)



The Object Compounds



Example No.	R^1
1 (1)	
1 (2)	
1 (3)	
1 (4)	
1 (5)	
1 (6)	
1 (7)	
1 (8)	

Example No.	R^1
1 (9)	
1 (10)	
1 (11)	
1 (12)	
1 (13)	
1 (14)	
1 (15)	

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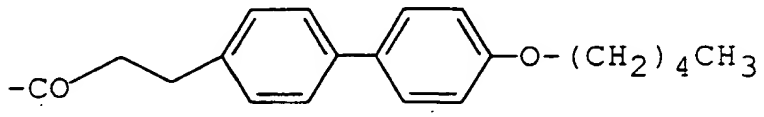
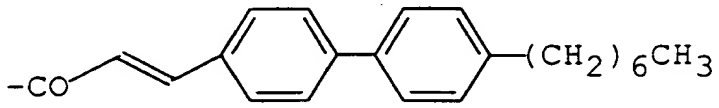
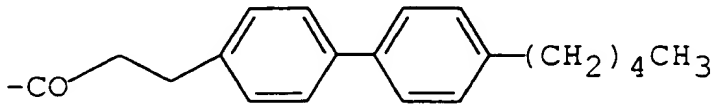
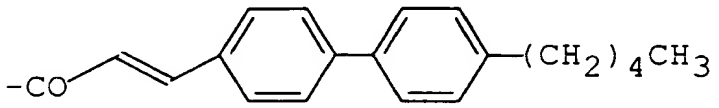
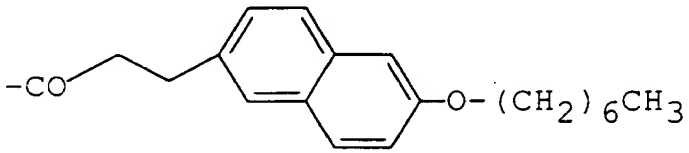
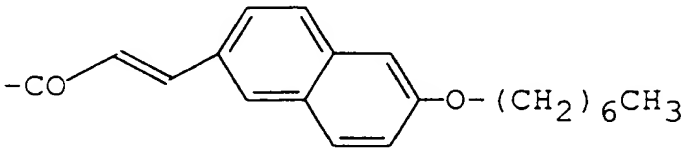
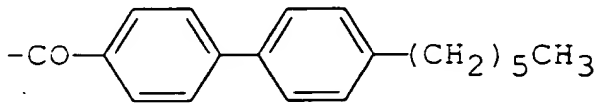
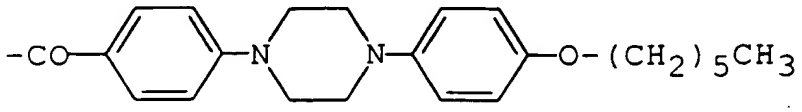
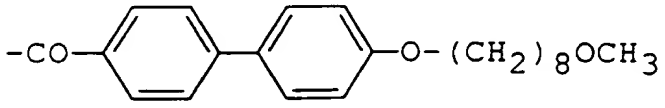
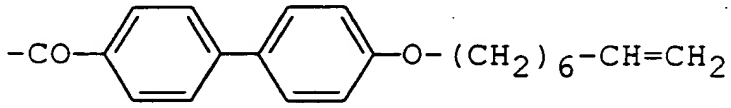
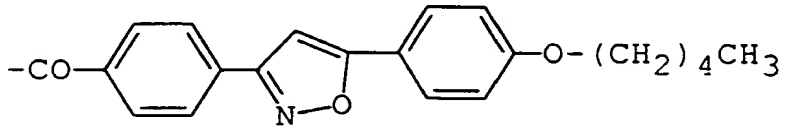
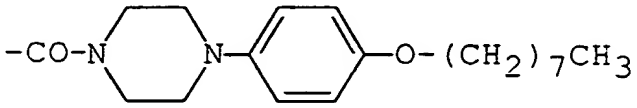
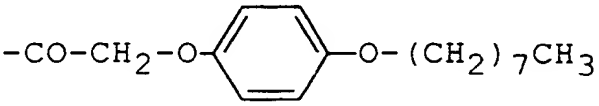
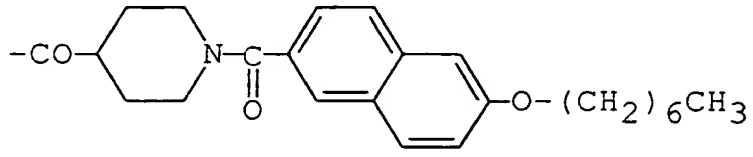
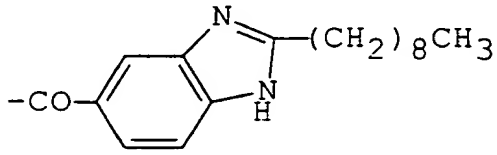
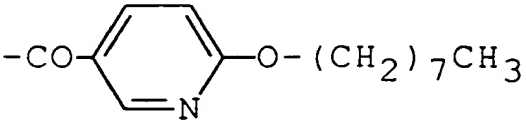
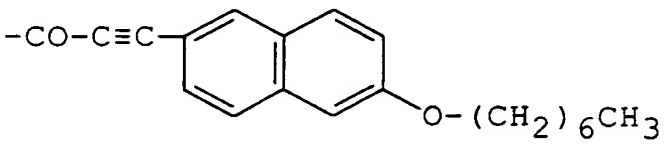
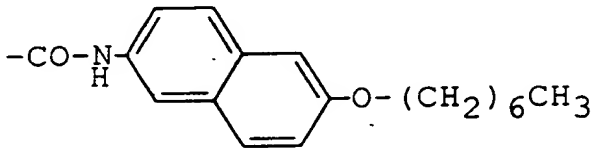
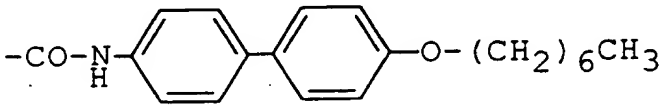
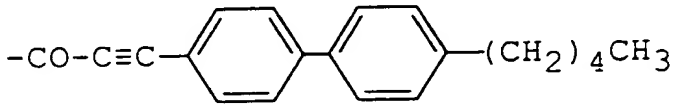
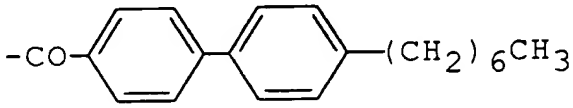
1 (16)	
1 (17)	
1 (18)	
1 (19)	
1 (20)	
1 (21)	
1 (22)	
1 (23)	
1 (24) major product	

Example No.	R^1
1 (24) minor product	
1 (25)	
2	
3 (1)	
3 (2)	
3 (3)	
3 (4)	
3 (5)	

Example No.	R^1
4 (1)	
4 (2)	
5	
6	

Example 1(1)

To a solution of The Starting Compound (1 g) and 1-(6-octyl-oxymethylpicolinoyl)benzotriazole 3-oxide (0.399 g) in N,N-dimethylformamide (10 ml) was added 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Trademark : prepared by Dow Chemical)) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel·ODS-AM·S-50) (Trademark : prepared by Yamamura

Chemical Lab.) eluting with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give The Object Compound (1).

IR (KBr) : 3347, 1664, 1629, 1517 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 0.98 (3H, d, J=6.7Hz), 1.09 (3H, d, J=6.0Hz), 1.2-1.47 (10H, m), 1.47-1.67 (2H, m), 1.67-2.06 (3H, m), 2.06-2.5 (4H, m), 3.19 (1H, m), 3.53 (2H, t, J=6.4Hz), 3.5-3.85 (2H, m), 3.85-4.7 (13H, m), 5.35 (11H, m), 5.56 (1H, d, J=5.7Hz), 6.73 (1H, d, J=8.3Hz), 6.83 (1H, d, J=8.3Hz), 6.89 (1H, s), 7.05 (1H, s), 7.11 (1H, s), 7.32 (1H, m), 7.43 (1H, d, J=8.5Hz), 7.63 (1H, d, J=7.3Hz), 7.85-8.13 (4H, m), 8.66 (1H, d, J=7.8Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1228 (M^++Na)

Elemental Analysis Calcd. for $C_{50}H_{72}N_9O_{22}SNa \cdot 6H_2O$:
C 45.49, H 6.44, N 9.59

Found : C 45.89, H 6.52, N 9.69

Example 1 (2)

The Object Compound 1 (2) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3353, 1666, 1510, 1236 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.06 (3H, d, J=5.8Hz), 1.2-1.5 (10H, m), 1.55-2.05 (5H, m), 2.11-2.7 (4H, m), 3.0-3.3 (5H, m), 3.3-3.5 (4H, m), 3.6-4.5 (15H, m), 4.6-5.6 (12H, m), 6.6-7.2 (10H, m), 7.2-7.5 (3H, m), 7.81 (2H, d, J=8.8Hz), 8.05 (1H, d, J=8.7Hz), 8.28 (1H, d, J=8.7Hz), 8.41 (1H, d, J=6.7Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1373 (M^++Na)

Elemental Analysis Calcd. for $C_{60}H_{83}N_{10}O_{22}SNa \cdot 4H_2O$:
C 50.63, H 6.44, N 9.84
Found : C 50.59, H 6.59, N 9.79

Example 1 (3)

The Object Compound 1 (3) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3350, 1664, 1627, 1047 cm^{-1}

NMR (DMSO-d_6, δ) : 0.96 (3H, d, J=6.6Hz), 1.08 (3H, d, J=5.7Hz), 1.15-1.53 (8H, m), 1.55-2.1 (9H, m), 2.1-2.45 (3H, m), 2.5-2.7 (1H, m), 3.18 (1H, m), 3.6-3.83 (2H, m), 3.83-4.6 (17H, m), 4.7-5.4 (11H, m), 5.51 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.83 (1H, d, J=8.2Hz), 6.85 (1H, s), 7.03 (2H, d, J=8.4Hz), 7.05 (1H, s), 7.30 (1H, s), 7.2-7.5 (2H, m), 7.67 (2H, d, J=8.4Hz), 7.71 (2H, d, J=7.4Hz), 7.94 (1H, s), 7.96 (2H, d, J=7.4Hz), 8.06 (1H, d, J=8.0Hz), 8.25 (1H, d, J=6.7Hz), 8.50 (1H, s), 8.74 (1H, d, J=6.7Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1356 (M^++Na)

Elemental Analysis Calcd. for $C_{58}H_{76}N_{11}O_{22}SNa \cdot 4H_2O$:
C 49.53, H 6.02, N 10.95
Found : C 49.26, H 6.22, N 10.77

Example 1 (4)

The Object Compound 1 (4) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3350, 1660, 1631, 1047 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.9Hz), 0.97 (3H, d, J=6.6Hz), 1.09 (3H, d, J=5.3Hz), 1.2-1.5 (10H, m), 1.37 (6H, s), 1.55-2.0 (5H, m), 2.1-2.6 (4H, m), 3.16 (1H, m), 3.73 (2H, m), 3.89 (2H, t, J=6.3Hz), 3.95-4.49 (11H, m), 4.68-5.21 (10H, m), 5.25 (1H, d, J=4.1Hz), 5.53 (1H, d,

J=5.7Hz), 6.73 (1H, d, J=8.2Hz), 6.75-6.85 (4H, m), 6.91 (1H, d, J=8.2Hz), 7.05 (1H, s), 7.15 (1H, s), 7.3-7.5 (2H, m), 7.9-8.2 (3H, m), 8.84 (1H, s)

FAB-MASS : e/z = 1271 (M^++Na)

Elemental Analysis Calcd. For $C_{53}H_{77}N_8O_{23}SNa \cdot 4H_2O$:
C 48.18, H 6.48, N 8.48
Found : C 48.04, H 6.51, N 8.38

Example 1 (5)

The Object Compound 1 (5) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 1666, 1629, 1222 cm^{-1}

NMR (DMSO-d_6, δ) : 0.85 (3H, t, J=6.6Hz), 0.9-1.12 (6H, m), 1.12-1.52 (13H, m), 1.52-1.93 (5H, m), 2.08-2.55 (4H, m), 3.16 (1H, m), 3.6-5.3 (26H, m), 5.49 + 5.54 (1H, d, J=5.8Hz, mixture of diastereomer), 6.60-7.1 (7H, m), 7.04 (1H, s), 7.1 (1H, m), 7.2-7.5 (2H, m), 7.9-8.43 (3H, m), 8.83 (1H, s)

FAB-MASS : e/z = 1257 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{75}N_8O_{23}SNa \cdot 3H_2O$:
C 48.44, H 6.33, N 8.69
Found : C 48.16, H 6.51, N 8.53

Example 1 (6)

The Object Compound 1 (6) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3349, 1666, 1629, 1259 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 0.9 (3H, d, J=5.7Hz), 0.96 (3H, d, J=6.7Hz), 1.1-1.55 (19H, m), 1.55-2.0 (5H, m), 2.0-2.47 (4H, m), 2.65-3.25 (3H, m), 3.5-5.13 (27H, m), 5.17 (1H, d, J=3.2Hz), 5.24 (1H, d, J=4.5Hz), 5.38 (1H, d, J=5.9Hz), 6.5-6.9 (5H, m), 6.9-7.1 (3H, m), 7.2-

7.46 (2H, m), 7.7-8.1 (3H, m), 8.83 (1H, s)

FAB-MASS : e/z = 1368 (M^++Na)

Elemental Analysis Calcd. for $C_{58}H_{84}N_9O_{24}SNa \cdot 5H_2O$:

C 48.50, N 6.60, N 8.78

Found : C 48.47, H 6.83, N 8.78

Example 1 (7)

The Object Compound 1 (7) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3350, 1666, 1502, 1199 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.6Hz), 0.97 (3H, d, J=6.7Hz), 1.06 (3H, d, J=5.7Hz), 1.2-1.5 (10H, m), 1.55-2.0 (5H, m), 2.1-2.6 (4H, m), 3.17 (1H, m), 3.7-4.5 (15H, m), 4.7-5.22 (10H, m), 5.24 (1H, d, J=4.4Hz), 5.60 (1H, d, J=5.9Hz), 6.68-7.03 (8H, m), 7.04 (1H, s), 7.2-7.42 (2H, m), 7.85-8.1 (3H, m), 8.83 (1H, s)

FAB-MASS : e/z = 1229 (M^++Na)

Elemental Analysis Calcd. for $C_{50}H_{71}N_8O_{23}SNa \cdot 5H_2O$:

C 46.29, H 6.29, N 8.64

Found : C 46.39, H 6.05, N 8.72

Example 1 (8)

The Object Compound 1 (8) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3350, 1666, 1631, 1513 cm^{-1}

NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=6.2Hz), 0.97 (3H, d, J=6.7Hz), 1.04 (3H, d, J=5.7Hz), 1.2-1.58 (8H, m), 1.58-2.0 (5H, m), 2.0-2.6 (4H, m), 3.17 (1H, m), 3.6-4.5 (15H, m), 4.63-5.33 (13H, m), 5.53 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.82 (1H, d, J=8.2Hz), 6.84 (1H, s), 6.95-7.52 (7H, m), 7.66 (1H, d, J=7.6Hz), 7.7-7.9 (3H, m), 8.05 (1H, d, J=9.1Hz), 8.15 (1H, d, J=7.6Hz), 8.85 (1H, s)

FAB-MASS : e/z = 1279 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{73}N_8O_{23}SNa \cdot 5H_2O$:
C 48.14, H 6.21, N 8.32

Found : C 48.43, H 6.28, N 8.30

Example 1 (9)

The Object Compound 1 (9) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3347, 2956, 1664, 1633, 1508, 1444, 1268, 1047 cm^{-1}

NMR (DMSO-d_6, δ) : 0.9-1.1 (9H, m), 1.06 (3H, d, J=5.9Hz), 1.3-1.5 (8H, m), 1.6-2.0 (7H, m), 2.1-2.4 (3H, m), 2.5-2.6 (1H, m), 3.1-3.3 (1H, m), 3.6-4.4 (17H, m), 4.7-5.0 (8H, m), 5.09 (1H, d, J=5.5Hz), 5.16 (1H, d, J=3.1Hz), 5.24 (1H, d, J=4.5Hz), 6.73 (1H, d, J=8.2Hz), 6.8-6.9 (2H, m), 6.98 (1H, d, J=8.3Hz), 7.05 (1H, d, J=1.7Hz), 7.3-7.6 (5H, m), 8.08 (1H, d, J=8.9Hz), 8.25 (1H, d, J=8.4Hz), 8.54 (1H, d, J=7.5Hz), 8.83 (1H, s)

FAB-MASS : e/z = 1257 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{75}N_8O_{23}SNa \cdot 4H_2O$:
C 47.78, H 6.40, N 8.57

Found : C 47.88, H 6.71, N 8.53

Example 1 (10)

The Object Compound 1 (10) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3350, 2931, 1664, 1625, 1529, 1440, 1276, 1226, 1047 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.8Hz), 0.97 (3H, d, J=6.7Hz), 1.12 (3H, d, J=5.9Hz), 1.2-1.5 (10H, m), 1.6-2.1 (5H, m), 2.1-2.4 (4H, m), 3.1-3.3 (1H, m), 3.5-4.6 (15H, m), 4.7-5.0 (3H, m), 5.0-5.2 (7H, m), 5.27 (1H, d, J=4.4Hz), 5.55

(1H, d, J=5.7Hz), 6.73 (1H, d, J=8.2Hz), 6.8-7.0 (2H, m), 7.0-7.2 (4H, m), 7.3-7.6 (2H, m), 7.90 (1H, d, J=8.8Hz), 8.0-8.2 (2H, m), 8.8-8.9 (2H, m), 9.06 (1H, d, J=7.2Hz)

FAB-MASS : e/z = 1281 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{71}N_8O_{24}SNa \cdot 5H_2O$:
C 47.18, H 6.05, N 8.30
Found : C 46.97, H 6.27, N 8.22

Example 1 (11)

The Object Compound 1 (11) was obtained according to a similar manner to that of Example 1 (1).

NMR (DMSO-d_6, δ) : 0.87-1.05 (6H, m), 1.10 (3H, d, J=5.7Hz), 1.3-1.5 (4H, m), 1.6-1.9 (5H, m), 2.2-2.5 (3H, m), 2.6 (1H, m), 3.1-3.2 (1H, m), 3.7-4.5 (15H, m), 4.8-5.1 (8H, m), 5.09 (1H, d, J=5.64Hz), 5.16 (1H, d, J=3.2Hz), 5.26 (1H, d, J=4.2Hz), 5.52 (1H, d, J=6.0Hz), 6.73 (2H, d, J=8.4Hz), 6.8-6.9 (2H, m), 7.0-7.1 (3H, m), 7.2-7.4 (4H, m), 7.6-7.8 (6H, m), 8.11 (1H, d, J=8.4Hz), 8.29 (1H, d, J=8.4Hz), 8.51 (1H, d, J=7.7Hz), 8.85 (1H, s)

FAB-MASS : e/z = 1273 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{22}SNa \cdot 4H_2O$:
C 49.92, H 6.02, N 8.47
Found : C 49.79, H 6.14, N 8.45

Example 1 (12)

The Object Compound 1 (12) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3330, 2929, 1670, 1629, 1533, 1440, 1280, 1226, 1045, 804 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.9Hz), 1.2-1.6 (10H, m), 1.6-2.0 (5H, m), 2.1-2.5 (4H, m), 3.1-

3.3 (1H, m), 3.6-4.5 (15H, m), 4.8-5.1 (9H, m), 5.17 (1H, d, J=3.0Hz), 5.25 (1H, d, J=4.5Hz), 5.56 (1H, d, J=5.6Hz), 6.73 (1H, d, J=8.2Hz), 6.83 (1H, d, J=6.8Hz), 7.1-7.2 (3H, m), 7.3-7.5 (3H, m), 7.85 (1H, d, J=8.8Hz), 8.0-8.2 (3H, m), 8.84 (1H, s), 8.96 (1H, d, J=7.2Hz)

FAB-MASS : e/z = 1269 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{71}N_8O_{22}S_2Na \cdot 4H_2O$:
C 47.34, H 6.04, N 8.49
Found : C 47.21, H 5.96, N 8.41

Example 1 (13)

The Object Compound 1 (13) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3345, 2927, 1664, 1629, 1515, 1442, 1274, 1047 cm^{-1}

NMR (DMSO-d_6, δ) : 0.85 (3H, t, J=6.7Hz), 0.97 (3H, d, J=6.7Hz), 1.10 (3H, d, J=5.9Hz), 1.2-1.4 (10H, m), 1.5-2.5 (8H, m), 2.46 (3H, s), 2.69 (2H, t, J=7.7Hz), 3.1-3.4 (2H, m), 3.6-4.5 (17H, m), 4.8-5.2 (8H, m), 6.7-7.0 (3H, m), 7.05 (1H, d, J=1.7Hz), 7.14 (1H, s), 7.3-7.6 (5H, m), 8.0-8.2 (2H, m), 8.47 (1H, d, J=7.0Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1251 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{73}N_8O_{22}SNa \cdot 3H_2O$:
C 49.61, H 6.21, N 8.73
Found : C 49.88, H 6.44, N 8.74

Example 1 (14)

The Object Compound 1 (14) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3340, 1672, 1627, 1542, 1513, 1440, 1268, 1045 cm^{-1}

NMR (DMSO-d_6, δ) : 0.84 (3H, t, J=6.7Hz), 0.94 (3H, d, J=6.7Hz), 1.07 (3H, d, J=6.0Hz), 1.2-1.4

(12H, m), 1.6-2.0 (5H, m), 2.1-2.4 (3H, m), 2.6 (1H, m), 2.96 (2H, t, J=7.4Hz), 3.1-3.3 (1H, m), 3.6-4.5 (13H, m), 4.7-5.2 (11H, m), 5.50 (1H, d, J=5.7Hz), 6.73 (1H, d, J=8.2Hz), 6.8-6.9 (2H, m), 7.04 (1H, s), 7.2-7.5 (3H, m), 7.72 (1H, d, J=8.5Hz), 7.91 (1H, d, J=8.4Hz), 8.05 (1H, d, J=8.4Hz), 8.2-8.4 (1H, m), 8.80 (1H, d, J=7.7Hz), 8.83 (1H, s)

FAB-MASS : e/z = 1252 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{72}N_9O_{22}SNa \cdot 6H_2O$:
C 46.67, H 6.33, N 9.42
Found : C 46.72, H 6.53, N 9.45

Example 1 (15)

The Object Compound 1 (15) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3350, 2935, 1664, 1627, 1517, 1446, 1251, 1045 cm^{-1}

NMR (DMSO-d_6, δ) : 0.90-1.1 (6H, m), 1.10 (3H, d, J=5.9Hz), 1.2-1.4 (6H, m), 1.6-2.4 (8H, m), 2.6-2.7 (1H, m), 3.1-3.3 (1H, m), 3.7-4.5 (16H, m), 4.7-5.4 (11H, m), 5.51 (1H, d, J=5.6Hz), 6.7-7.0 (3H, m), 7.0-7.6 (7H, m), 7.74 (1H, d, J=8.6Hz), 8.0-8.4 (5H, m), 8.7-8.8 (1H, m), 8.84 (1H, s)

FAB-MASS : e/z = 1301 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_{10}O_{22}SNa \cdot 6H_2O$:
C 47.62, H 6.03, N 10.01
Found : C 47.65, H 6.03, N 10.03

Example 1 (16)

The Object Compound 1 (16) was obtained according to a similar manner to that of Example 1 (1).

IR (Nujol) : 3353, 1668, 1627, 1540, 1515, 1500 cm^{-1}

NMR (DMSO-d_6, δ) : 0.80-1.00 (6H, m), 1.06 (3H, d, J=5.9Hz), 1.20-1.53 (4H, m), 1.60-1.95 (5H, m),

2.00-2.65 (8H, m), 2.80 (2H, t, J=7.5Hz), 3.05-3.45 (1H, m), 3.50-3.85 (2H, m), 3.90-4.48 (11H, m), 4.65-5.38 (11H, m), 5.47 (1H, d, J=6.0Hz), 6.65-6.90 (2H, m), 6.90-7.10 (2H, m), 7.10-7.65 (11H, m), 7.90-8.25 (2H, m), 8.30 (1H, d, J=7.8Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1275.3 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}SNa \cdot 3H_2O$:
C 50.53, H 6.09, N 8.57

Found : C 50.48, H 6.39, N 8.57

Example 1 (17)

The Object Compound 1 (17) was obtained according to a similar manner to that of Example 1 (1).

IR (Nujol) : 3351, 1656, 1623, 1538, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.8Hz), 1.15-1.40 (8H, m), 1.50-2.00 (5H, m), 2.10-2.48 (4H, m), 2.52-2.70 (2H, m), 3.05-3.28 (1H, m), 3.60-4.50 (13H, m), 4.70-5.20 (9H, m), 5.25 (1H, d, J=4.6Hz), 5.52 (1H, d, J=6.0Hz), 6.68-6.92 (4H, m), 7.04 (1H, d, J=1.0Hz), 7.22-7.50 (5H, m), 7.55-7.82 (7H, m), 8.14 (1H, d, J=8.4Hz), 8.31 (1H, d, J=8.4Hz), 8.54 (1H, d, J=7.7Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1285 (M^++Na)

Example 1 (18)

The Object Compound 1 (18) was obtained according to a similar manner to that of Example 1 (1).

IR (Nujol) : 3351, 1668, 1627, 1540, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87 (3H, t, J=6.8Hz), 0.96 (3H, d, J=6.7Hz), 1.06 (3H, d, J=5.8Hz), 1.17-1.48 (4H, m), 1.50-1.95 (5H, m), 2.05-2.70 (8H, m), 2.70-2.95 (2H, m), 3.05-3.30 (1H, m), 3.60-3.90

(2H, m), 3.90-4.50 (11H, m), 4.65-5.10 (9H, m), 5.15 (1H, d, J=3.2Hz), 5.23 (1H, d, J=4.2Hz), 5.48 (1H, d, J=6.0Hz), 6.67-6.90 (3H, m), 7.03 (1H, d, J=1.5Hz), 7.15-7.80 (11H, m), 8.00-8.20 (2H, m), 8.29 (1H, d, J=7.8Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1259 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{21}SNa \cdot 6H_2O$:
C 50.30, H 6.52, N 8.53
Found : C 50.42, H 6.50, N 8.45

Example 1 (19)

The Object Compound 1 (19) was obtained according to a similar manner to that of Example 1 (1).

IR (Nujol) : 3351, 1668, 1652, 1623, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.07 (3H, d, J=6.0Hz), 1.25-1.45 (4H, m), 1.50-2.00 (5H, m), 2.05-2.48 (4H, m), 2.50-2.75 (2H, m), 3.60-4.50 (13H, m), 4.68-5.25 (10H, m), 5.27 (1H, d, J=4.5Hz), 5.53 (1H, d, J=6.0Hz), 6.67-6.98 (4H, m), 7.05 (1H, d, J=1.0Hz), 7.22-7.58 (5H, m), 7.58-7.90 (7H, m), 8.16 (1H, d, J=9.0Hz), 8.34 (1H, d, J=8.4Hz), 8.57 (1H, d, J=7.7Hz), 8.85 (1H, s)

FAB-MASS : e/z = 1258 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{71}N_8O_{21}SNa \cdot 5H_2O$:
C 49.84, H 6.15, N 8.45
Found : C 49.77, H 6.27, N 8.39

Example 1 (20)

The Object Compound 1 (20) was obtained according to a similar manner to that of Example 1 (1).

IR (Nujol) : 3353, 1670, 1629, 1540, 1508 cm^{-1}

NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=6.5Hz), 0.97 (3H, d, J=6.8Hz), 1.04 (3H, d, J=5.9Hz), 1.20-1.58 (8H, m), 1.60-1.96 (5H, m), 2.08-2.60 (6H, m),

2.70-3.00 (2H, m), 3.00-3.40 (1H, m), 3.60-3.85 (2H, m), 3.85-4.50 (13H, m), 4.50-5.60 (12H, m), 6.65-6.90 (3H, m), 7.00-7.15 (3H, m), 7.18-7.50 (4H, m), 7.59 (1H, s), 7.62-7.78 (2H, m), 7.95-8.20 (2H, m), 8.30 (1H, d, J=7.7Hz), 8.83 (1H, s)

FAB-MASS : e/z = 1277 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{75}N_8O_{22}SNa \cdot 4H_2O$:
C 49.77, H 6.30, N 8.44
Found : C 49.67, H 6.31, N 8.40

Example 1 (21)

The Object Compound 1 (21) was obtained according to a similar manner to that of Example 1 (1).

IR (Nujol) : 3351, 1654, 1623, 1538, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87 (3H, t, J=6.7Hz), 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.9Hz), 1.20-1.58 (8H, m), 1.66-1.95 (5H, m), 2.10-2.60 (4H, m), 3.09-3.30 (1H, m), 3.58-4.60 (15H, m), 4.69-5.20 (10H, m), 5.24 (1H, d, J=4.5Hz), 5.51 (1H, d, J=6.0Hz), 6.68-6.95 (4H, m), 7.04 (1H, d, J=1.0Hz), 7.10-7.73 (7H, m), 7.73-7.90 (2H, m), 7.98 (1H, d, J=1.9Hz), 8.10 (1H, d, J=8.4Hz), 8.32 (1H, d, J=8.4Hz), 8.50 (1H, d, J=7.7Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1275 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{22}SNa \cdot 5H_2O$:
C 50.38, H 6.38, N 8.55
Found : C 49.98, H 6.37, N 8.41

Example 1 (22)

The Object Compound 1 (22) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3340, 2931, 1664, 1627, 1531, 1444, 1278, 1047 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.6Hz), 0.96 (3H, d, J=6.8Hz), 1.08 (3H, d, J=5.9Hz), 1.2-1.4 (6H, m), 1.5-1.7 (2H, m), 1.7-2.1 (3H, m), 2.2-2.4 (3H, m), 2.6-2.7 (3H, m), 3.1-3.2 (1H, m), 3.7-4.6 (13H, m), 4.78 (1H, d, J=6.0Hz), 4.8-5.1 (1H, m), 5.09 (1H, d, J=5.6Hz), 5.16 (1H, d, J=3.2Hz), 5.24 (1H, d, J=4.4Hz), 5.52 (1H, d, J=6.0Hz), 6.73 (1H, d, J=8.2Hz), 6.83 (2H, d, J=8.3Hz), 7.05 (1H, s), 7.3-7.5 (5H, m), 7.65 (2H, d, J=8.2Hz), 7.74 (2H, d, J=8.4Hz), 7.98 (2H, d, J=8.4Hz), 8.11 (1H, d, J=8.4Hz), 8.31 (1H, d, J=8.4Hz), 8.79 (1H, d, J=7.7Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1245 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{71}N_8O_{21}SNa \cdot 4H_2O$:
C 50.07, H 6.15, N 8.65
Found : C 50.26, H 6.44, N 8.67

Example 1 (23)

The Object Compound 1 (23) was obtained according to a similar manner to that of Example 1 (1).

NMR (DMSO-d_6, δ) : 0.91 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.8Hz), 1.05 (3H, d, J=5.6Hz), 1.2-1.5 (6H, m), 1.6-2.1 (5H, m), 2.1-2.7 (4H, m), 3.0-3.5 (9H, m), 3.6-4.5 (15H, m), 4.6-5.6 (11H, m), 6.73 (1H, d, J=8.2Hz), 6.8-6.9 (4H, m), 6.95 (2H, d, J=8.6Hz), 7.02 (2H, d, J=9.2Hz), 7.04 (1H, s), 7.2-7.5 (3H, m), 7.82 (2H, d, J=8.6Hz), 8.06 (1H, d, J=8Hz), 8.25 (1H, d, J=6.7Hz), 8.43 (1H, d, J=6.7Hz), 8.85 (1H, s)

IR (KBr) : 3350, 1668, 1629, 1510 cm^{-1}

FAB-MASS : e/z = 1345 (M+Na)

Elemental Analysis Calcd. for $C_{58}H_{79}N_{10}O_{22}SNa \cdot 6H_2O$:
C 48.67, H 6.41, N 9.78
Found : C 48.80, H 6.46, N 9.82

Example 1 (24)

The Object Compound 1 (24) was obtained according to a similar manner to that of Example 1 (1).

Major product

IR (KBr) : 3350, 1668, 1631, 1047 cm^{-1}

NMR (DMSO-d_6, δ) : 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.7Hz), 1.2-1.6 (10H, m), 1.6-2.4 (8H, m), 2.5-2.7 (1H, m), 3.18 (1H, m), 3.21 (3H, s), 3.29 (2H, t, J=6.4Hz), 3.6-3.83 (2H, m), 3.83-4.6 (13H, m), 4.7-5.4 (11H, m), 5.51 (1H, d, J=5.9Hz), 6.73 (1H, d, J=8.2Hz), 6.83 (1H, d, J=8.2Hz), 6.85 (1H, s), 7.04 (2H, d, J=8.4Hz), 7.06 (1H, s), 7.31 (1H, s), 7.2-7.5 (2H, m), 7.67 (2H, d, J=8.4Hz), 7.71 (2H, d, J=8.4Hz), 7.96 (2H, d, J=8.4Hz), 8.06 (1H, d, J=8Hz), 8.25 (1H, d, J=6.7Hz), 8.74 (1H, d, J=6.7Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1319 (M+Na)

Elemental Analysis Calcd. for $C_{57}H_{77}N_8O_{23}SNa \cdot 4H_2O$:
C 49.99, H 6.26, N 8.18
Found : C 49.74, H 6.27, N 8.06

Minor product

IR (KBr) : 3350, 1668, 1631 cm^{-1}

NMR (DMSO-d_6, δ) : 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.7Hz), 1.2-1.6 (6H, m), 1.6-2.1 (7H, m), 2.1-2.5 (3H, m), 2.5-2.7 (1H, m), 3.18 (1H, m), 3.6-3.8 (2H, m), 3.8-4.6 (13H, m), 4.6-5.2 (12H, m), 5.26 (1H, d, J=4.6Hz), 5.53 (1H, d, J=5.8Hz), 5.6-6.0 (1H, m), 6.73 (1H, d, J=8.2Hz), 6.83 (1H, d, J=8.3Hz), 6.85 (1H, s), 7.04 (2H, d, J=8.5Hz), 7.06 (1H, s), 7.30 (1H, s), 7.2-7.5 (2H, m), 7.68 (2H, d, J=8.5Hz), 7.72 (2H, d, J=8.5Hz), 7.96 (2H, d, J=8.5Hz), 8.06

(1H, d, J=8Hz), 8.25 (1H, d, J=6.7Hz), 8.74 (1H, d, J=6.7Hz), 8.85 (1H, s)

FAB-MASS : e/z = 1287 (M+Na)

Elemental Analysis Calcd. for $C_{56}H_{73}N_8NaO_{22}S \cdot 7H_2O$:
C 48.34, H 6.30, N 8.05
Found : C 48.19, H 6.19, N 7.99

Example 1 (25)

The object Compound 1 (25) was obtained according to a similar manner to that of Example 1 (1).

IR (KBr) : 3350, 2935, 2873, 1668, 1629, 1538, 1506, 1438, 1257, 1049 cm^{-1}

NMR (DMSO-d_6, δ) : 0.9-1.0 (6H, m), 1.08 (3H, d, J=5.7Hz), 1.2-1.6 (4H, m), 1.6-2.0 (5H, m), 2.1-2.4 (3H, m), 2.5-2.6 (1H, m), 3.1-3.2 (1H, m), 3.6-4.6 (15H, m), 4.7-5.2 (10H, m), 5.26 (1H, d J=4.5Hz), 5.55 (1H, d, J=5.9Hz), 6.7-6.9 (3H, m), 7.0-7.6 (7H, m), 7.85 (2H, d, J=8.6Hz), 7.9-8.2 (4H, m), 8.26 (1H, d, J=7.7Hz), 8.8-9.0 (2H, m)

FAB-MASS : 1314.3 $(M+Na)^+$

Elemental Analysis Calcd. for $C_{56}H_{70}N_9O_{23}NaS \cdot 7H_2O$:
C 47.42, H 5.97, N 8.89
Found : C 47.33, H 5.85, N 8.73

Example 2

To a solution of The Starting Compound (1 g) and succinimido 4-(4-octyloxyphenyl)piperazine-1-carboxylate (0.45 g) in N,N-dimethylformamide (10 ml) was added 4-dimethylaminopyridine (0.141 g), and stirred for 5 days at 50°C. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchage resin (DOWEX-50WX4) eluting with water. The

fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel·ODS-AM·S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give crude The Object Compound (23). The powder of crude The Object Compound (23) was purified by preparative HPLC utilizing a C_{18} μ Bondapak resin (Waters Associates, Inc.) which was eluted with a solvent system comprised of (acetonitrile-pH 3 phosphate buffer = 40:60) at a flow rate of 80 ml/minute using a Shimadzu LC-8A pump. The column was monitored by a UV detector set at 240 um. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel·ODS-AM·S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (23) (60 mg).

IR (KBr) : 3347, 1629, 1511, 1245 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 0.95 (3H, d, J=6.8Hz), 1.06 (3H, d, J=5.9Hz), 1.2-1.5 (10H, m), 1.55-1.92 (5H, m), 2.0-2.65 (4H, m), 2.8-3.05 (5H, m), 3.2-4.47 (17H, m), 4.6-5.6 (12H, m), 6.6-7.0 (7H, m), 7.03 (1H, s), 7.2-7.5 (3H, m), 7.9-8.3 (3H, m), 8.84 (1H, s)

FAB-MASS : e/z = 1297 (M^++Na)

Elemental Analysis Calcd. for $C_{54}H_{79}N_{10}O_{22}SNa·6H_2O·CH_3CN$:
C 47.22, H 6.65, N 10.82
Found : C 47.58, H 7.05, N 10.85

Example 3 (1)

To a suspension of 1-hydroxybenzotriazole (0.53 g) and 2-(4-octyloxyphenoxy)acetic acid (1 g) in dichlormethane (30 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (0.886 g), and stirred for 3 hours at ambient temperature. The reaction mixture was added to water. The organic layer was taken, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[2-(4-octyloxyphenoxy)acetyl]benzotriazole 3-oxide (892 mg). To a solution of 1-[2-(4-octyloxyphenoxy)acetyl]benzotriazole 3-oxide (892 mg) in N,N-dimethylformamide (18 ml) was added 4-(N,N-dimethylamino)pyridine (0.297 g), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was added to water, and subjected to ion-exchange column chromatography on DOWEX-50WX4, and eluted with water. The fractions containing the object compound were combined, and subjected to column chromatograph on ODS (YMC-gel·ODS-AM·S-50), and eluted with 50% methanol aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove methanol. The residue was lyophilized to give The Object Compound (24) (1.75 g).

IR (KBr) : 3350, 1666, 1629, 1228 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.9Hz), 0.95 (3H, d, J=6.7Hz), 1.04 (3H, d, J=5.7Hz), 1.15-1.5 (10H, m), 1.55-2.0 (5H, m), 2.05-2.5 (4H, m), 3.16 (1H, m), 3.72 (2H, m), 3.88 (3H, t, J=6.3Hz), 4.41 (2H, s), 3.93-4.6 (11H, m), 4.69-5.25 (10H, m), 5.28 (1H, d, J=4.3Hz), 5.57 (1H, d, J=5.7Hz), 6.73 (1H, d, J=8.2Hz), 6.8-7.0 (5H, m), 7.04 (1H, s), 7.09 (1H, s), 7.3-7.4

(2H, m), 7.92-8.17 (2H, m), 8.29 (1H, d, J=7.5Hz), 8.84 (1H, s)

FAB-MASS : e/z = 1243 (M^++Na)

Elemental Analysis Calcd. for $C_{51}H_{73}N_8O_{23}SNa \cdot 4H_2O$:
C 47.36, H 6.31, N 8.66
Found : C 47.22, H 6.44, N 8.37

Example 3 (2)

The Object Compound 3 (2) was obtained according to a similar manner to that of Example 3 (1).

IR (KBr) : 3350, 2933, 1664, 1628, 1446, 1205, 1045 cm^{-1}

NMR (DMSO-d_6, δ) : 0.8-1.1 (9H, m), 1.2-2.0 (19H, m), 2.1-2.3 (3H, m), 3.6-3.8 (4H, m), 3.9-4.4 (13H, m), 4.6-5.0 (8H, m), 5.07 (1H, d, J=5.6Hz), 5.14 (1H, d, J=3.2Hz), 5.23 (1H, d, J=4.3Hz), 5.46 (1H, d, J=6.7Hz), 6.7-6.9 (3H, m), 7.04 (1H, s), 7.2-7.5 (6H, m), 7.8-8.0 (3H, m), 8.05 (1H, d, J=8.4Hz), 8.2-8.4 (2H, m), 8.83 (1H, s)

FAB-MASS : e/z = 1360 (M^++Na)

Elemental Analysis Calcd. for $C_{59}H_{80}N_9O_{23}SNa \cdot 6H_2O$:
C 48.99, H 6.41, N 8.72
Found : C 48.92, H 6.37, N 8.64

Example 3 (3)

The Object Compound 3 (3) was obtained according to a similar manner to that of Example 3 (1).

IR (KBr) : 3350, 2927, 1668, 1627, 1535, 1515, 1452, 1440, 1286, 1045 cm^{-1}

NMR (DMSO-d_6, δ) : 0.83 (3H, t, J=6.7Hz), 0.95 (3H, d, J=6.7Hz), 1.07 (3H, d, J=5.9Hz), 1.2-1.4 (12H, m), 1.6-2.0 (5H, m), 2.1-2.4 (3H, m), 2.6 (1H, m), 2.82 (2H, t, J=7.4Hz), 3.1-3.2 (1H, m), 3.6-4.5 (13H, m), 4.7-5.2 (11H, m), 5.4-5.6 (1H,

m), 6.72 (1H, d, J=8.2Hz), 6.82 (2H, d, J=8.1Hz), 7.03 (1H, s), 7.2-7.4 (3H, m), 7.47 (1H, d, J=8.5Hz), 7.69 (1H, d, J=8.5Hz), 8.1-8.2 (2H, m), 8.23 (1H, d, J=8.4Hz), 8.62 (1H, d, J=7.8Hz), 8.83 (1H, s)

FAB-MASS : e/z = 1251 (M^++Na)

Elemental Analysis Calcd. for $C_{52}H_{73}N_{10}O_{21}SNa \cdot 5H_2O$:
C 47.34, H 6.34, N 10.61
Found : C 47.30, H 6.45, N 10.45

Example 3 (4)

The Object Compound 3 (4) was obtained according to a similar manner to that of Example 3 (1).

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.8Hz), 0.96 (3H, t, J=6.7Hz), 1.05 (3H, t, J=5.8Hz), 1.2-1.5 (10H, m), 1.6-2.0 (5H, m), 2.2-2.4 (3H, m), 2.5-2.6 (1H, m), 3.1-3.2 (1H, m), 3.7-4.5 (15H, m), 4.7-5.0 (8H, m), 5.10 (1H, d, J=5.6Hz), 5.17 (1H, d, J=3.1Hz), 5.26 (1H, d, J=4.5Hz), 5.52 (1H, d, J=5.8Hz) 6.73 (1H, d, J=8.2Hz), 6.8-7.0 (3H, m), 7.04 (1H, s), 7.2-7.4 (3H, m), 8.0-8.3 (3H, m), 8.68 (1H, d, J=2.3Hz), 8.7-8.8 (1H, m), 8.85 (1H, m)

FAB-MASS : e/z = 1214 (M^++Na)

Elemental Analysis Calcd. for $C_{49}H_{70}N_9O_{22}SNa \cdot 4H_2O$:
C 46.55, H 6.22, N 9.97
Found : C 46.29, H 6.18, N 9.71

Example 3 (5)

The Object Compound 3 (5) was obtained according to a similar manner to that of Example 3 (1).

IR (Nujol) : 3342, 2210, 1668, 1623 cm^{-1}

NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=6.7Hz), 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d, J=6.7Hz), 1.20-1.60 (8H, m), 1.60-2.00 (5H, m), 2.05-2.50 (4H, m),

3.05-3.30 (1H, m), 3.60-4.60 (15H, m), 4.65-5.18 (10H, m), 5.24 (1H, d, J=4.5Hz), 5.58 (1H, d, J=6.0Hz), 6.68-7.10 (4H, m), 7.15-7.65 (5H, m), 7.80-8.30 (6H, m), 8.84 (1H, s), 9.18 (1H, d, J=7.7Hz)

FAB-MASS : e/z = 1273.5 (M^++Na)

Example 4 (1)

To a solution of 6-heptyloxy-2-naphthoic acid (0.358 g) and triethylamine (0.174 ml) in N,N-dimethylformamide (10 ml) was added diphenylphosphoryl azide (0.4 ml), and stirred for an hour at ambient temperature. Then, the reaction mixture was stirred for an hour at 100°C. After cooling, to the reaction mixture was added The Starting Compound (1 g) and 4-(N,N-dimethylamino)pyridine (0.140 g), and stirred for 10 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The powder was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fractions containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel·ODS-AM·S-50) eluting with 50% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (29) (0.832 g).

IR (KBr) : 3350, 1664, 1629, 1546, 1240 cm^{-1}

NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=6.6Hz), 0.97 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.9Hz), 1.2-1.55 (8H, m), 1.55-2.0 (5H, m), 2.1-2.5 (4H, m), 3.18 (1H, m), 3.6-3.8 (3H, m), 3.9-4.5 (13H, m), 4.7-4.95 (3H, m), 5.0-5.3 (7H, m), 5.59 (1H, d, J=5.8Hz), 6.52 (1H, d, J=8.1Hz), 6.73 (1H, d,

J=8.2Hz), 6.83 (1H, d, J=8.2Hz), 6.90 (1H, s), 7.0-7.15 (3H, m), 7.20 (1H, s), 7.27-7.4 (3H, m), 7.6-7.7 (2H, m), 7.87 (1H, s), 7.95-8.2 (2H, m), 8.69 (1H, s), 8.85 (1H, s)

FAB-MS : e/z = 1264 (M^++Na)

Elemental Analysis Calcd. for $C_{53}H_{72}N_9O_{22}SNa \cdot 5H_2O$:
C 47.78, H 6.20, N 9.46
Found : C 47.65, H 6.42, N 9.34

Example 4 (2)

The Object Compound 4 (2) was obtained according to a similar manner to that of Example 4 (1).

IR (KBr) : 3350, 1666, 1629, 1537, 1240 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87 (3H, t, J=6.7Hz), 0.97 (3H, d, J=6.7Hz), 1.09 (3H, d, J=5.8Hz), 1.2-1.55 (8H, m), 1.55-2.0 (5H, m), 2.07-2.6 (4H, m), 3.18 (1H, m), 3.6-3.85 (3H, m), 3.9-4.5 (13H, m), 4.7-4.98 (3H, m), 5.0-5.3 (7H, m), 5.57 (1H, d, J=5.9Hz), 6.50 (1H, d, J=8.1Hz), 6.73 (1H, d, J=8.2Hz), 6.82 (1H, dd, J=8.2 and 1.7Hz), 6.87 (1H, s), 6.97 (2H, d, J=8.8Hz), 7.05 (1H, d, J=1.7Hz), 7.10 (1H, s), 7.23-7.43 (2H, m), 7.38 (2H, d, J=8.8Hz), 7.50 (2H, d, J=8.8Hz), 7.52 (2H, d, J=8.8Hz), 8.0-8.15 (2H, m), 8.65 (1H, s), 8.84 (1H, s)

FAB-MASS : e/z = 1290 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{74}N_9O_{22}SNa \cdot 7H_2O$:
C 47.38, H 6.36, N 9.04
Found : C 47.67, H 6.53, N 9.03

Example 5

A solution of The Starting Compound (2.45 g), 3-[4-(4-pentylphenyl)phenyl]propiolic acid (0.90 g), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl) (0.59 g) and triethylamine (0.43 ml) in N,N-

dimethylformamide (50 ml) was stirred for 15 hours at ambient temperature. The reaction mixture was diluted with ethyl acetate, and the resultant precipitate was collected by filtration, and washed in turn with ethyl acetate and diisopropyl ether, and dried under reduced pressure. The powder was dissolved in water, and was subjected to column chromatography on ion exchange resin (DOWEX-50WX4 (Na form, 50 ml)) eluting with water. The fractions containing the object compound were combined, and subjected to reversed phase chromatography on ODS (YMC-gel·ODS-AM·S-50, 50 ml) eluting with (water : acetonitrile = 10:0 - 7:3, V/V). The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (31) (1.53 g).

IR (Nujol) : 3351, 2212, 1668, 1627 cm^{-1}

NMR (DMSO-d_6, δ) : 0.87 (3H, t, J=6.5Hz), 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.8Hz), 1.20-1.50 (4H, m), 1.50-2.00 (5H, m), 2.03-2.55 (4H, m), 2.62 (2H, t, J=7.5Hz), 3.17 (1H, t, J=8.4Hz), 3.55-4.57 (15H, m), 4.65-5.13 (9H, m), 5.16 (1H, d, J=3.2Hz), 5.24 (1H, d, J=4.5Hz), 5.58 (1H, d, J=5.8Hz), 6.67-6.90 (3H, m), 6.93-7.10 (2H, m), 7.15-7.50 (4H, m), 7.50-7.90 (6H, m), 8.06 (1H, d, J=8.4Hz), 8.15 (1H, d, J=7.7Hz), 8.84 (1H, s), 9.19 (1H, d, J=7.1Hz)

FAB-MASS : e/z = 1255 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{69}N_8O_{21}SNa·4H_2O$:
C 50.61, H 5.95, N 8.58
Found : C 50.47, H 6.00, N 8.54

Example 6

To a suspension of 1-hydroxybenzotriazole (501 mg) and 4-(4-heptylphenyl)benzoic acid (1 g) in dichloromethane (30 ml) was added 1-ethyl-3-(3'-

dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (839 mg), and stirred for 3 hours at ambient temperature. The reaction mixture was added to water. The organic layer was separated, and dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was evaporated under reduced pressure to give 1-[4-(4-heptylphenyl)benzoyl]benzotriazole 3-oxide. To a solution of The Starting Compound (2.49 g) and 1-[4-(4-heptylphenyl)benzoyl]benzotriazole 3-oxide in N,N-dimethylformamide (25 ml) was added 4-(N,N-dimethylamino)pyridine (381 mg), and stirred for 12 hours at ambient temperature. The reaction mixture was pulverized with ethyl acetate. The precipitate was collected by filtration, and dried under reduced pressure. The residue was dissolved in water, and subjected to column chromatography on ion exchange resin (DOWEX-50WX4) eluting with water. The fraction containing the object compound were combined, and subjected to column chromatography on ODS (YMC-gel·ODS-AM·S-50) eluting with 30% acetonitrile aqueous solution. The fractions containing the object compound were combined, and evaporated under reduced pressure to remove acetonitrile. The residue was lyophilized to give The Object Compound (32) (1.99 g).

IR (Nujol) : 3350, 2852, 1749, 1621, 1457, 1376, 1045 cm^{-1}

NMR (DMSO-d_6, δ) : 0.86 (3H, t, J=6.7Hz), 0.96 (3H, d, J=6.7Hz), 1.08 (3H, d, J=5.9Hz), 1.5-1.7 (2H, m), 1.7-2.2 (3H, m), 2.2-2.5 (3H, m), 2.6-2.8 (3H, m), 3.1-3.2 (1H, m), 3.7-4.6 (13H, m), 4.7-5.2 (8H, m), 5.12 (1H, d, J=5.5Hz), 5.18 (1H, d, J=2.9Hz), 5.27 (1H, d, J=4.4Hz), 5.54 (1H, d, J=5.8Hz), 6.7-6.9 (3H, m), 7.05 (1H, s), 7.2-7.4 (5H, m), 7.65 (2H, d, J=8.0Hz), 7.74 (2H, d, J=8.3Hz), 7.98 (2H, d, J=8.3Hz), 8.11

(1H, d, J=8.7Hz), 8.28 (1H, d, J=8.4Hz), 8.78 (1H, d, J=7.3Hz), 8.85 (1H, s)

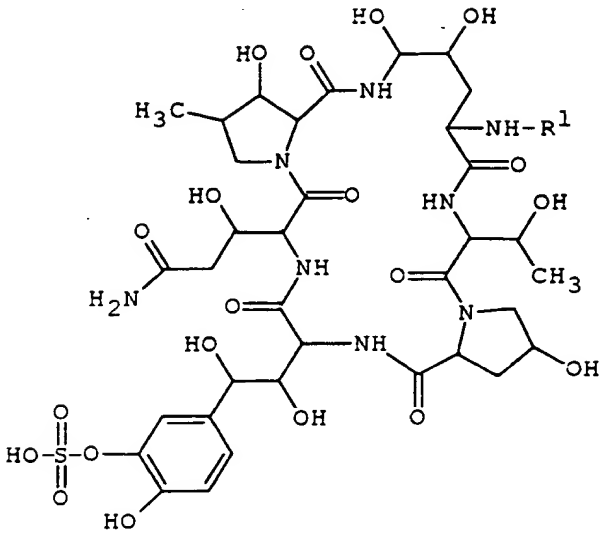
FAB-MASS : e/z = 1259 (M^++Na)

Elemental Analysis Calcd. for $C_{55}H_{73}N_8O_{21}SNa \cdot 5H_2O$:
C 49.77, H 6.30, N 8.44

Found : C 49.98, H 6.44, N 8.41

What we claim is :

1. A polypeptide compound of the following general formula :



[I]

wherein R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s)

which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s);

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy;

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclic(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

aryloxy(lower)alkanoyl which may have one or more suitable substituent(s);

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s); and

a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline having higher alkoxy and lower alkoxy carbonyl;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing at least one oxygen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl,

higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atoms which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting

of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

3. A compound of claim 1, wherein

R^1 is ar(lower)alkenoyl substituted with aryl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthyl(lower)alkenoyl which may have 1 to 3 higher alkoxy;

lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

ar(C_2-C_6)alkanoyl substituted with aryl having 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower

alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy.

4. A compound of claim 1, wherein

R^1 is aroyl substituted with heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

aroyl substituted with aryl having heterocyclic(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl.

5. A compound of claim 1, wherein

R^1 is aryloxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl,

higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

6. A compound of claim 1, wherein
R^1 is ar(lower)alkoxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

7. A compound of claim 1, wherein
R^1 is arylamino(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

8. A compound of claim 2, wherein
R^1 is lower alkanoyl substituted with pyridyl which may have 1 to 3 substituent(s) selected from the

group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with 1,2,3,4-tetrahydroisoquinoline having higher alkoxy and lower alkoxy carbonyl;

lower alkanoyl substituted with coumarin which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with benzothiophenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with benzo[b]furanyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher

alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with benzooxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with benzimidazolyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkoyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

lower alkanoyl substituted with saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl

having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

9. A compound of claim 3, wherein

R^1 is phenyl(lower)alkenoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthyl(lower)alkenoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthyl(lower)alkenoyl which may have 1 to 3 higher alkoxy;

lower alkynoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, phenyl substituted with

phenyl having lower alkoxy, phenyl substituted with phenyl having higher alkoxy, naphthyl substituted with phenyl having lower alkoxy, naphthyl substituted with phenyl having higher alkoxy, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

phenyl(C_2-C_6)alkanoyl substituted with phenyl which has 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, napthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthyl(C_2-C_6)alkanoyl substituted with phenyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy.

10. A compound of claim 4, wherein

R^1 is benzoyl substituted with saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected form the group consisting of lower

alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

benzoyl substituted with unsaturated 5-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s) which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl, having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthoyl substituted with saturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

benzoyl substituted with phenyl having unsaturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom substituted

with higher alkoxy;

benzoyl substituted with phenyl having lower alkoxy(higher)alkoxy;

benzoyl substituted with phenyl having lower alkenyl(lower)alkoxy;

benzoyl substituted with 2 lower alkoxy;

benzoyl substituted with phenyl having lower alkyl;

naphthoyl substituted with phenyl having lower alkyl;

benzoyl substituted with phenyl having higher alkyl;

naphthoyl substituted with phenyl having higher alkyl.

11. A compound of claim 5, wherein

R^1 is phenyloxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

napthyloxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having

lower alkyl, and oxo.

12. A compound of claim 6, wherein

R^1 is phenyl(lower)alkoxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthyl(lower)alkoxy(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

phenylamino(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

naphthylamino(lower)alkanoyl which may have 1 to 3 substituent(s) selected from the group

consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo.

13. A compound of claim 10, wherein

R^1 is benzoyl substituted with piperazine which may have 1 to 3 substituent(s) selected form the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

benzoyl substituted with isoxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkoxy, higher alkoxy, lower alkyl, higher alkyl, higher alkoxy(lower)alkyl, phenyl having lower alkoxy, phenyl having higher alkoxy, naphthyl having lower alkoxy, naphthyl having higher alkoxy, phenyl having lower alkyl, phenyl having higher alkyl, naphthoyl having higher alkoxy, phenyl substituted with phenyl having lower alkyl, and oxo;

benzoyl substituted with phenyl having triazolyl(higher)alkoxy;

benzoyl substituted with phenyl having lower alkoxy(higher)alkoxy;

benzoyl substituted with phenyl having lower

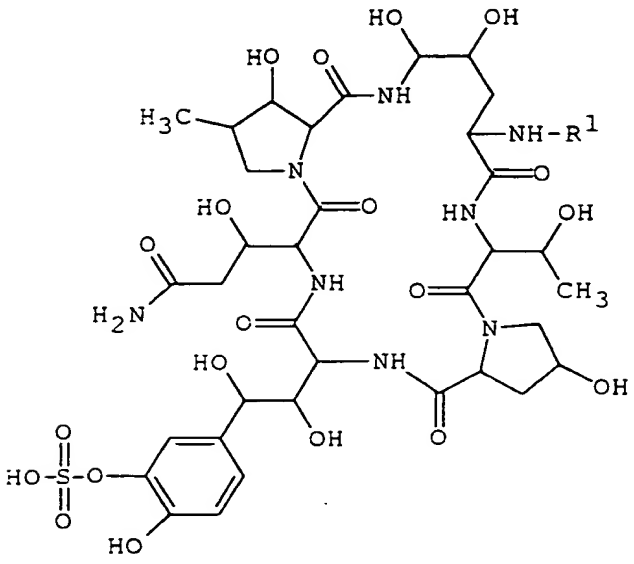
alkenyl(lower)alkoxy;

benzoyl substituted with 2 lower alkoxy;

benzoyl substituted with phenyl having lower alkyl;

benzoyl substituted with phenyl having higher alkyl.

14. A process for the preparation of a polypeptide compound of the formula [I] :



[I]

wherein R^1 is lower alkanoyl substituted with unsaturated 6-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with 1,2,3,4-tetrahydro-isoquinoline having higher alkoxy;

lower alkanoyl substituted with unsaturated condensed heterocyclic

group containing at least one oxygen atom which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 1 to 3 sulfur atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with unsaturated condensed heterocyclic group containing 2 or more nitrogen atom(s) which may have one or more suitable substituent(s);

lower alkanoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing at least one nitrogen atom which may have one or more suitable substituent(s);

ar(lower)alkenoyl substituted with aryl which may have one or more suitable substituent(s);

naphthyl(lower)alkenoyl which may have one or more higher alkoxy;

lower alkynoyl which may have one or more suitable substituent(s);

ar(C_2-C_6)alkanoyl substituted with aryl having one or more suitable substituent(s);

(C_2-C_6)alkanoyl substituted with naphthyl having higher alkoxy;

aroyl substituted with heterocyclic group which may have one or more suitable substituent(s);

aroyl substituted with aryl having heterocyclic(higher)alkoxy;

aroyl substituted with aryl having lower alkoxy(higher)alkoxy;

aroyl substituted with aryl having lower alkenyl(lower)alkoxy;

aroyl substituted with 2 lower alkoxy;

aroyl substituted with aryl having lower alkyl;

aroyl substituted with aryl having higher alkyl;

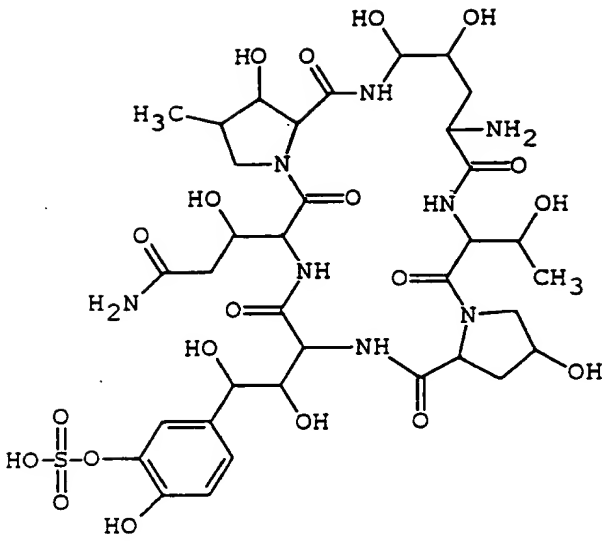
aryloxy(lower)alkanoyl which may have one or more suitable substituent(s);

ar(lower)alkoxy(lower)alkanoyl which may have one or more suitable substituent(s);

arylamino(lower)alkanoyl which may have one or more suitable substituent(s); and

a pharmaceutically acceptable salt thereof, which comprises

1) reacting a compound of the formula :

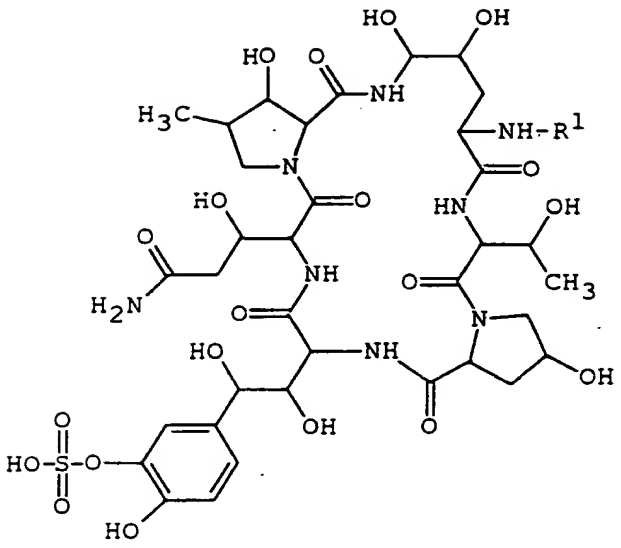


[II]

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula :

$$R^1\text{-OH} \qquad [III]$$

wherein R^1 is defined above,
or its reactive derivative at the carboxy group or a salt thereof, to give a compound [I] of the formula:



[I]

wherein R^1 is defined above,
or a salt thereof.

15. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

16. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

17. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

18. A method for the prophylactic and/or the therapeutic treatment of diseases caused by pathogenic microorganism which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.